Available online on 15.2.2025 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

Open Access

Review Article

Statistical Forecasting Of Drug-Drug Interactions Using Medicines' Physiological Similarity

Rajesh Mishra[1*], Manu Dwivedi[2], Anubhav Dubey[2], Richard Owusu Nyarko[3], Mamta Kumari[4], Ajay Kumar Tripathi[5],Ateet Srivastava[6]

[1]Associate Professor, Swami Vivekananda College of Pharmacy Bhopal.
[2]Department of Pharmacy, Maharana Pratap College of Pharmacy, Kothi Mandhana, Kanpur, Uttar Pradesh, India.
[3]Faculty of Health Sciences Ghana Christian University College Accra Ghana.
[4]Department of Pharmacy, Harcourt Butler Technical University, Kanpur, Uttar Pradesh, India.
[5]Professor, Department of Pharmacy, Vidya Bhavan College of Pharmacy, Kanpur, Uttar Pradesh, India.
[6]Assistant Professor, Department of Pharmacy, S.J. Institute, Kanpur, Uttar Pradesh, India.

A B S T R A C T

Taking several drugs at once is a typical practice that raises the possibility of side effects and drug interactions(DDIs). Ensuring patient safety and the effectiveness of treatment methods relies heavily on the prediction and detection of DDIs. To forecast DDIs from drug structures and/or functions, many computational approaches have been used. A computer technique for DDIs prediction based on drug functional similarity is shown here. We established the model using essential biological components such as transporters, targets, enzymes, and carriers (CTET). It We applied it to 21,189 authorized medications. DDIs were determine. We determined the DDIs by gathering all the CTETs associated with each medication and then constructing the corresponding binary vectors. molarity tests to identify DDIs. Inner product-based similarity measures (IPSMs) produced the best prediction values among the similarity approaches that were considered. Researchers looked at 2,394,766 possible drug-pair interactions in total. The program may predict more than 250,000 DDIs with unknown causes. We conclude that the present technique is a general in silico strategy for DDI identification that is both simple and rapid, and we recommend it. In the future, we want to see this suggested strategy implemented as a realistic methodology for DDI identification using pharmacological functional similarities.

Keywords: Pharmacological, Methodology, Targets, Enzymes, Prediction.

A R T I C L E I N F O: Received 10 Nov.2024; Review Complete15 Jan 2025; Accepted 09 Feb.2025. ; Available online15 Feb. 2025

Cite this article as:
Mishra R, Dwivedi M, Dubey A, Nyarko RO, Kumari M, Tripathi AK, Srivastava A, Statistical Forecasting Of Drug-Drug Interactions Using Medicines' Physiological Similarity, Asian Journal of Pharmaceutical Research and Development. 2025; 13(1):217-230,
DOI: http://dx.doi.org/10.22270/ajprd.v13i1.1529

*Address for Correspondence:
Rajesh Mishra[1*], Associate Professor, Swami Vivekananda College of Pharmacy Bhopal

INTRODUCTION

One prominent cause of avoidable adverse events is drug-drug interactions (DDIs), which may occur accidentally or due to poor management. There is a growing concern about DDIs, which may cause an exacerbation of side effects or even a loss of therapeutic effectiveness due to the aging population and the increasing prevalence of polypharmacotherapy. Because of the Well-designed preclinical and clinical DDI investigations are necessary throughout drug development and, often, even after marketing approval. This highlights the need of adjusting prescription dosages to DDI concerns[1-10].

Additionally, accessible databases, clinical decision support systems, and modelling studies are necessary for better clinical decision-making. In the late 90s and early 2000s, serious safety issues led to the removal of many DDIs from the marketplace, such as Cerivastatin, Terfenadine, Cisapride, and Mibefradil. Regulators have recently revised their recommendations for drug interaction studies in response to these regrettable occurrences and the rapid growth of scientific understanding of DDI processes and dangers. The

US Food and medication Administration (FDA) last released its recommendations for clinical medication interaction studies, while the European Medicines Agency (EMA) is presently updating its guidelines in 2017. The focus of these recommendations is on research for new pharmaceuticals; however, the ideas presented here are applicable to existing pharmaceuticals as well. Thanks to the aforementioned advancements, drug development and DDI research have come a long way[11-18]. As a result, the number of drugs requiring withdrawal from circulation due to DDIs has significantly decreased. Additionally, doctors typically have all the information they need to manage DDIs, which are caused by the inhibition or stimulation of key transporters and other enzymes, including The FDA authorizes medications for distribution based on enzymes known as cytochrome P450 (CYP). The FDA authorized 34 medications in 2017. Of these, the FDA found 5 to be strong inhibitors of Cytochrome3A, OATP1B1, or breast cancer resistance protein (BCRP), and no strong inducers. We found the remaining 34 medications to be sensitive substrates of CYP3A. The majority of dangerous drug interactions occur when one medication alters another's metabolism or transporter-mediated disposition, resulting in changes in the plasma concentrations of the victim drug [19-25]. It is known that induction raises metabolic elimination and lowers victim concentrations. On the other hand, blocking drug metabolism or transporter-dependent elimination often raises victim concentrations. Such interactions may, at worst, cause drug exposure to vary by a factor of several hundred. In the last ten years, a number of review papers have focused on specific aspects of clinical DDI research. This article gives an overview of the methods used in clinical DDI studies to look into a drug's part in pharmacokinetic DDIs that happen when drug-metabolizing enzymes and/or transporters are turned on or off. We then try to highlight particular factors that have been important to us based on our personal experience with these types of studies. We look at more than just the regulatory guidelines because we want to address specific concerns about complicated DDIs, pharmacogenetics, methodological traps, and how to interpret DDI results. This is because most of the methodology described in the guidelines can be used for investigations that happen during the drug development process [26-30].

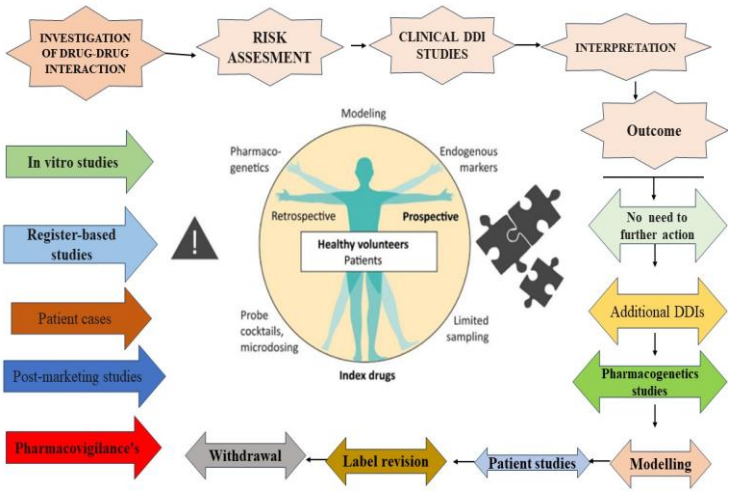

Figure 1: illustrates the analysis of DDIs. (a) There are a number of possible origins for signals that might indicate a DDI. (a) Thorough evaluation of signals is necessary before taking any further action. (c) A prospective crossover trial using index medications, often conducted in healthy volunteers, is the gold standard for clinical DDI research. The interpretation of the findings defines the study's (e) implications [6].

Table 1: Provides some things to think about and have in place before doing interventional DDI research, as well as examples of potential problems with DDI studies

Common requirements for a DDI	Possible problems with DDI
Overarching concerns with the design	
If there are no safety issues, healthy volunteers	Dangerous medications used to those experiencing good health
Concerns about patient safety or the patient's clinical emphasis	Potential sources of bias and confounding in cohort studies of patients
Design for crossover	Bias might result from using a parallel group design.
Excessive washing to eradicate residual effects	Inadequate flushing out (such as when a slowly removed metabolite is still there).
Methods of blinding and placebo control (for example, while assessing pharmacodynamic end goals)	
Adjustments to one's diet as needed	
Carefully prepared to cover more than 80% to 90% of the AUC for the offending drug and its metabolites; kept and evaluated in the correct manner;	Deterioration of analytes during storage or analysis, an inaccurate or insensitive analytical procedure
Keeping an eye on the pharmacokinetics of the offender (adherence,	No evidence of perpetrator exposure found

exposure measurement, presence after washout)	
Evaluation of pharmacodynamics	Neglected pharmacodynamic evaluations
DNA extracts	
Biomarker samples in some instances	
Important background information for design safety concerns	Negligible screening standards that might have negative consequences
Rigid prohibitions (such as during pregnancy or in cases of contraindication)	
Genotyping, laboratory testing, clinical history, and physical examination	Lack of adequate follow-up (unwanted side effects of medication)
Keep an eye on things and make sure you follow up enough	
Measures taken and actions taken to prevent negative consequences, even in the most extreme situations issue with DDI	
It is recommended that blood samples do not surpass the amount of blood that is donated.	Underwhelming power Agent that inhibits
A potential rise in AUC of more than five times depends on the index inhibitor's selectivity and potency.	Weak inhibition due to too low a dosage
Depending on tolerability, administered at a clinically meaningful dosage	Unlikely dosage for clinical use Time between doses is either too short or too lengthy to record maximum DDI.
Dosage for steady-state effects, including induction and inhibition that vary with time	
Substratum of the victim	Insensitivity (especially when not taken into account while interpreting)
Conditional sensitivity of test substrate	Absence of bias (especially when not accounted for in the analysis)
Established substrate selectivity	Using a short-acting or "presystemic" inhibitor on a victim with a long half-life
Preferable with a high first-pass and a short half-life	
The use of metabolic ratio monitoring	In order to record the maximum DDI, the victim must not get a large dosage of medication too soon (or too late) after the offender.
Dose, assuming the worst-case scenario	Dangerous medications used to those experiencing good health

Table 2: Possible CYP enzyme index substrates: characteristics

Enzyme	**Substrate**	**Sensitivity**	**enzymes/transporters**	**F**	**$t_{1/2}$(h)**	**Remarks**	**E/F[b]**
CYP1A2	Agomelatine	+		0.05	1–2	Limitedavailabilityinsomecountries	
CYP2B6	Bupropion	+	11β-HSD1	0.9	11	Hydroxy bupropiontobupropion	E
CYP2C8	Amodiaquine	N/A		N/A	5	LimitedDDIdata Limited availability, metabolite, $t_{1/2}$>100hours	E
CYP2C9	(S)-Warfarin	+		0.93	21–43	Bleedingrisk	E/F
CYP2C19	Lansoprazole	+	CYP3A4	0.81	0.9	Delayedabsorption	F
CYP2D6	Desipramine	+	CYP3A4	0.38	28	Limitedavailabilityinsome countries	E/F
CYP3A4	Buspirone	+	CYP3A4	0.04	2.4	SensitivetointestinalCYP3A4 inhibition	E/F

THE CLINICAL DDI STUDY DESIGN

General clinical DDI research design concerns

The best research design for pharmacokinetic DDIs is fundamentally defined by the study's hypotheses and aims. It is common practice to regularly evaluate interaction risk during medication development based on past knowledge (Figure 1). When a medication starts clinical development, the evaluation usually depends on in vitro, animal and computational data, when combined with clinical data, it rapidly becomes more accurate[31-40]. Examinations of demographic data, case reports, or other in vitro data that are conducted retrospectively may spark DDI investigations if the

medicine is already on the market or in later phases of clinical development. There are two ways to test a drug's effects on Transporters and Enzymes have a role in drug metabolism, either as substrates (victim drugs) or as inducers or inhibitors (perpetrator drugs). For instance, in 2012–11, an epidemiologic study looked back at how often rhabdomyolysis happened in people who took cerivastatin and clopidogrel. This study led to more research, which found that clopidogrel blocks CYP2C8. Before beginning to draft a protocol for clinical DDI research, there are a number of design considerations and needs that must be carefully examined (Table 1). Clinical DDI research should ideally include healthy participants in a prospective crossover design. Because participants are also their own controls, the crossover design mitigates the impact of intraindividual variability. Furthermore, healthy patients with good kidney and liver function, no concurrent drug use, and no other interfering variables (such as smoking) show less interindividual variability. Typically, to show a clinically meaningful interaction in a in excellent health, a sample size of 10–12 persons is sufficient for two-way pharmacokinetic crossover DDI study among volunteers. However, to show that there is no DDI, a sample size that is 2-3 times bigger may be necessary. The washout interval between phases should be sufficiently lengthy to ensure the complete removal of all medicines, metabolites, and their effects before proceeding to the next phase of a crossover trial, particularly when dealing with powerful inhibitors that hinder their clearance[41-55]. In patient populations, DDI studies may be conducted when medication toxicity or side effects are a concern; however, a higher sample size is usually necessary owing to increased variability caused by different individual characteristics, especially when the design is based on parallel groups. Typically, a probe or index substrate for a certain pharmacokinetic pathway is used as the victim substance in a drug-induced inhibition or induction research (Table 2). The primary goal of these types of research is to aid in the discovery of new drugs by determining, using in vitro data, which enzymes the medicine inhibits most effectively. In order to uncover the most extreme example, it is recommended to deliver the to find the worst case, it is suggested to give the drug in question in several doses until the concentrations reach steady state at the highest levels used for therapy, while also testing its DDI potential as an inhibitor (Figure 2). extent of the interaction. This holds particularly true when the victim undergoes extensive first-pass metabolism and rapidly eliminates the inhibitor. For instance, by giving the inhibitor and victim drugs an hour apart, you can get the highest inhibitor concentrations at the inhibition site. On the other hand, evaluating induction effects requires to administer the drug over a long enough length of time to achieve almost complete induction. But when both induction and inhibition are viable options, it's reasonable to let the offender take the medicine for take the medicine for at least 12 hours before giving it to the victim. This will give the offender a chance to experience the entire induction effect. For example, when administered in vivo, the archetypal CYP inducer rifampin13 suppresses OATP1B1/1B3, but this effect disappears within Twelve hours. The clinical importance of the key enzymes and transporters involved may be documented when we utilize probe or index inhibitors to establish which pathways contribute to the drug's pharmacokinetics while examining it as a victim (Table 3). In these cases, it is common for a single, small dose of the victim medicine to be sufficient[56-60].To guarantee a big enough safety margin in drug exposure, it may be ethically required to provide even subtherapeutic amounts of medication to victims if a substantial interaction is anticipated. Should the victim medicine demonstrate This dosing technique may be extended to steady-state circumstances at clinically relevant concentrations by taking into account the time-dependent and dose-dependent pharmacokinetics. dosages, providing sufficient information. Conversely, a somewhat large victim drug dosage may be required to enable measurement of enzyme/transporter inducer concentrations in order to study their effects. Pharmacodynamic impact monitoring may be necessary to ensure safety and assess the DDI's therapeutic relevance. Pharmacodynamic end points are very useful when the victim drug has active metabolites, when the drug's behavior in certain organs is likely to change (like when it crosses the blood-brain barrier), or when the two drugs are likely to be given together in a clinical setting. Conducting double-blind treatment phases is crucial when employing subjective pharmacodynamic measures [61-65].

Characteristics of appropriate index substrates for medication-metabolizing enzymes

Table 2 shows that the DDI research index substrate's most crucial feature is that it is sensitive to the specific pharmacokinetic route being studied. In the case of enzymes that metabolize drugs, it is ideal for the enzyme to digest more than 80%. This enables the AUC, or area under the plasma concentration-time curve, increases fivefold when the enzyme is completely inhibited. Also, it's important to know the index substrate's various disposition processes inside and out, particularly if the offender may trigger interactions via other pathways. Additionally, the substrate's characteristics should allow for comprehensive pharmacokinetic parameter characterization in an experimental study. In order to shorten the time, it takes to collect samples (which is necessary to cover 80-90% of its whole AUC) and account for the washout period to be needless, it is crucial that the probe's elimination half-life (t1/2) be suitably short. In this opinion, desipramine, efavirenz, and warfarin are not at all suitable index substrates. An index drug with a short half-life and considerable first-pass metabolism is ideal if measuring a temporary impact on enzyme activity is crucial. The ideal index substrate has no influence on other medicines' pharmacokinetics and displays linear pharmacokinetics. Tolerability and non-toxicity are important considerations, with a safety margin large enough to account for many times greater variations in exposure. It's also helpful if an index substrate is easy to quantify, comes in the right doses, and is commercially available. Metabolite

standards are also useful. When faced with many equally acceptable substrate options for a given objective, the clinical relevance of each combination should be considered before making a final decision.
There are cytochrome P450 (CYP) enzymes that have sensitive and selective index substrates, like CYP1A2, CYP2D6, and CYP3A. Other CYP enzymes, like cytochrome 2A6, cytochrome 2B6, cytochrome 2C9, and cytochrome 2J2, do not (Table 2). It is possible to find sensitive index substrates; however, they may also serve as transporter protein substrates. For example, repaglinide and simvastatin are both very sensitive to OATP1B1/1B3, and CYP2C8 and CYP3A break down more than 80% of these drugs, respectively. Both of these medicines have a long history of usefulness as index substrates; therefore, their nonselectivity may be considered when drawing conclusions from the research. Little is known about non-CYP enzymes at this time, and even less is known about which ones have excellent probe substrates (Table 4). Lastly, a particular reaction may be used in place of a sensitive index substrate if one is not easily available or practicable [66-70].

Features of appropriate index compounds that inhibit or stimulate enzymes that are involved in the metabolism of drugs

Two of the most critical features of index inhibitors are selectivity and the degree of inhibition, after safety. According to the guidelines provided by the FDA and EMA, When a drug increases the AUC of a sensitive index substrate in a particular metabolic pathway by five times or more, it is deemed a potent index inhibitor (2, 3). This equates to a clearance inhibition of at least 80%. To supply a victim medication with strong inhibition, we must repeat the inhibitor dosage until we thoroughly describe the victim's AUC (Tables 1 and 3). This process typically requires approximately five half-lives for the inhibitor. Strong inhibition enhances exposure to potential side effects from drug interactions, particularly in cases when the victim's medicine does not depend on a specific elimination pathway. An ideal index inhibitor would be selective, meaning it would stop just one enzyme, such that the results could be confidently used to infer mechanisms. On the other hand, if the index inhibitor inhibits more than one enzyme or transporter, it is not possible to pinpoint the effects on victim medication pharmacokinetics to a single route without further research. Finally, the long half-life of the inhibitor severely hinders the necessary washout interval. For instance, in crossover experiments, fluoxetine is not the best index inhibitor of CYP2D6 because of its metabolite norfluoxetine's 4–16-day half-life and parent fluoxetine's 4–6-day half-life. While most CYP enzymes have decent inhibitors, CYP2A6, CYP2B6, and CYP2C9 do not have any well-documented potent or selective inhibitors (Table 3). For example, although large dosages of fluconazole effectively inhibit CYP2C9, they also have a profound effect on CYP3A4 and CYP2C19. Also, there aren't many good inhibitors for enzymes other than cytochrome P450 (CYP) phosphorylases. For example, the strongest DDIs known to target uridine 5′-diphosphate glucuronosyltransferase (UGT) can only increase AUC by two to three times (Table 4). In cases where there is a high likelihood of concurrent clinical usage, trials using moderate, weak, and nonselective inhibitors are particularly necessary[71-80].

Only a few compounds, like polycyclic aromatic hydrocarbon compounds, can turn on CYP2D6. Other than those, known drugs don't have much or any effect on it. However, certain conditions like pregnancy can increase its activity, and induction is typically highly nonselective compared to inhibition. Rifampin is often used as the standard inducer in clinical DDI studies because it works very well and is safer than other strong inducers like phenytoin and carbamazepine. In the same way that other substances that cause rifampin activates many enzymes and transporters involved in drug metabolism, similar to what happens during pregnancy X receptor-mediated induction. It strongly induces CYP3A in the intestines and liver. This makes it a useful tool for determining if a medicine is susceptible to severe enzyme induction. Be aware that rifampin has such a potent CYP3A-inducing effect that it may significantly raise the proportion of the medication metabolized by cytochrome 3A; as a result, even a drug whose elimination is typically mostly via no inducible or weakly inducible pathways becomes reliant on CYP3A [81-85].

Particular factors to take into account while conducting drug-drug interaction (DDI) research involving transporters

Based on the available information, it seems that out of the many transporters, at least P-glycoprotein (P-gp), OATP1B1, and BCRP are the three proteins that have a role in DDIs that are clinically meaningful. OAT1, OAT3, OATP1B3, OATP2B1, OCT2, MATE1, MATE2-K, OATP1B3, UAT2, and organic cation transporter (OCT) are additional proteins that could potentially be involved in DDIs. This is why studying drug transporters is a standard part of preclinical drug research. This gives a lot of information about how an investigational medication works as a substrate or inhibitor of various transporters. Based on the drug's in vitro research, clinical transporter DDI studies of transporter substrates should be explored site of action, elimination route, likelihood of concurrent use, safety concerns, and likelihood of adverse events, according to FDA guidelines for clinical DDI studies. For example, when it comes to DDIs mediated by P-gp and BCRP, the majority of the clinically significant ones (such as rosuvastatin for BCRP and aliskiren, dabigatran, digoxin, and fexofenadine for P-gp) work by blocking the small intestine's ability to absorb these drugs or, in rare instances, by biliary or renal excretion. Furthermore, there is only a small amount of data that suggests the blood-brain barrier is one potential site of P-gp-mediated DDIs.This implies that conducting DDI studies is necessary if P-gp-targeting drugs exhibit pharmacological or toxic effects at a location beyond the barrier. Current recommendations suggest that studies focusing on OATP1B1 or OATP1B3 might be warranted for drugs that target the liver or are removed via the liver. Drugs eliminated from the body via the kidneys may also need studies of OAT1, OCT2, or DDIs mediated by MATE. It is also necessary to take into account OCT1 and OATP2B1, as recent research has shown that they have a role in measuring hepatic and intestinal DDIs. If in vitro research deems the drug a transporter inhibitor, we can conduct clinical DDI investigations with potential concurrent substrate medicines susceptible to a clinically meaningful DDI, regardless of the road to eradication that the offender takes. Comparing DDI studies involving drug-metabolizing enzymes with those involving transporters presents some difficulties. The first is

that it difficult to generalize DDI study findings to other medications due to the absence of unique index substrates and inhibitors (Figure-2). Some drugs, such dabigatran etexilate, have the potential to act as particular P-gp substrates. Renal P-gp has little effect on its excretion, whereas P-gp restricts its absorption in the intestines. In addition, dabigatran is very mildly affected by P-gp inhibition at therapeutic levels; hence, not even the most potent P-gp inhibitors have managed to triple its AUC. Similar to how rosuvastatin, adefovir, ganciclovir, and famotidine are all documented BCRP substrates, dovetailed and metformin are examples of OCT2 or MATE transporters, and blockage of these transporters has only marginally affected these substances. Despite pitavastatin and simvastatin being moderately sensitive sub-states of OATP1B1 and 1B3, it remains uncertain if inhibiting a single transporter could increase the AUC of these drugs by more than five times. Most of the time, well-established transporter inhibitors aren't very selective and only inhibit to a small degree. Itraconazole, quinidine, verapamil, clarithromycin, and P-gp inhibitors can all stop cytochrome enzymes from working. Cyclosporine can stop cytochrome 3A4 along with BCRP, P-gp, and OATPs, and probenecid can only stop OATs 1 and 3. A potent inducer of drug-metabolizing enzymes, rifampin is an OATP inhibitor as well. It's possible for enzymes like ABCG2, CES1, cytochrome 2C9, cytochrome 2C19, cytochrome 2D6, cytochrome 3A4, cytochrome 3A5, DPYD, SLC22A1, SLCO1B1, TPMT, UGT1A1, UGT1A3, UGT2B10, and UGT2B17 to have a big effect on genes. If you think that these genes might be involved in the pharmacokinetics of the victim or perpetrator in a DDI study, you might want to look into genotyping for them. Differences in these genes could be used to separate subject groups in a genotype panel study [86-88].

Table 3: Features of potential CYP enzyme index inhibitors

Enzyme	Inhibitor	Dose administered during DDI studies	Strength	Additionally blocks	t1/2 (h)	Observations	E/Fc
Cytochrome 1A2	Fluvoxamine	25 dosages ranging from 100 mg/kg q.d. to 200 mg/kg b.i.d..	+	Cytochrome 2C19, Cytochrome 2D6, Cytochrome 3A4	15	An effective substrate metabolic ratio-based inhibitor of cytochrome 2B6 and cytochrome 2C19 The MBI is a powerful inhibitor of cytochrome 2C19.	F
Cytochrome 2B6	Ticlopidine	250 milligram/kilogram.i.d.	+	Cytochrome 2C19	98		E
Cytochrome 2C8	Clopidogrel	75 milligram/kilogram q.d. (first dose 300 milligram/kilogram)	+	Cytochrome 2B6, Cytochrome 2C19	6	Moderate Methylthiouraci (75 mg) each day is a cytochrome 2C8 inhibitor. Danger of bleeding	F
Cytochrome 2C9	Fluconazolee	200 milligram/kilogram q.d.	+	Cytochrome C19, v3A4	32	Strong Cytochrome 2C19 inhibitor	E/F
Cytochrome 2C19	Fluvoxaminee	25 milligram/kilogram b.i.d. to 100 milligram/kilogram q.d.	+	Cytochrome 1A2, Cytochrome 2D6, Cytochrome A4	15	Strong Cytochrome 1A2 inhibitor	F
Cytochrome 2D6	Fluoxetine	60 milligram/kilogram q.d.	+	Cytochrome 2C19	53	The half-life of norfluoxetine, a strong cytochrome 2C19 inhibitor, is 4-16 days.	E/F
Cytochrome 3A4	Clarithromycin	250–500 milligram/kilogram b.i.d.	+	Cytochrome 2C19, P-gp	3.3	MBI	E/F

Several options are provided in the table, which is based on sensitivity, selectivity, and safety, and includes all index inhibitors that have been recommended by the FDA and EMA. Much of the information comes from the University of Washington Metabolism and Transport Drug Interaction Database (Copyright University of Washington 1999-2019). Medication labels are an example of a secondary source (accessed January–February 2019).

Combinations of drugs and microdosing

To evaluate the activity of Among many transporters and enzymes involved in drug metabolism, the cocktail method administers more than one index substrate at the same time.

This allows for simultaneous investigation of a drug's role in many pharmacokinetic pathways within the framework of DDI investigations. To prevent cocktail components from interfering, each substrate must be delivered alone and in combination.Creating drug combinations and using very tiny doses of the substrate drugs (microdosing) to test drug transporters performance are two recent developments in this field. Safety and a lower chance of interactions between substrates are two benefits of microdosing. If the substrate exhibits nonlinear pharmacokinetics, it might be challenging to translate the results to dosages that are clinically meaningful. The last two decades have seen the creation of several phenotyping mixtures, including index substrates for variouscytochrome enzymes. Most suggested cocktails include index medicines for a maximum of six cytochrome enzymes, with cytochrome 1A2, cytochrome 2C9, cytochrome 2C19, cytochrome 2D6, cytochrome 2E1, and/or the most often used cytochrome is 3A4. Individual substrates are often somewhat selective for a certain enzyme, which allows for the drawing of mechanistic conclusions from the data. One issue with some older cocktails is the lack of availability of the index substrates recommended for them in certain regions. Substrates for cytochrome 1A2, cytochrome 2B6, cytochrome 2C9, cytochrome 2C19, cytochrome 2D6, and cytochrome 3A4 (fexofenadine is also an indicator for P-gp in the Geneva cocktail) are all part of two more modern cocktails that have been validated for DDI studies: the Basel cocktail and the Geneva cocktail. Because there aren't enough selective index substrates, creating drug transporter combinations is quite difficult. Digoxin, furosemide, metformin, and rosuvastatin were the original ingredients in the transporter cocktail for OATP1B1, OATP1B3, and BCRP. Combining the two medications improved rosuvastatin's peak plasma concentration (Cmax) and area under the curve (AUC) relative to taking either drug alone, as seen in the first experiment. After lowering the doses of metformin and furosemide, further studies showed that a combination of 0.25 mg digoxin, 1 mg furosemide, 10 mg metformin, and 10 mg rosuvastatin was safe and effective. So yet, we have no idea what the cocktail's sensitivity or the potential for reciprocal interactions in a scenario where an inhibitor under study elevates one component's exposure. Recently, DDI trials with known inhibitors tested a transporter combination that utilizes microdosing. The microdose cocktail had 10 micrograms of midazolam (CYP3A4), 375 micrograms of dabigatran etexilate (P-gp), 10 micrograms of pitavastatin (OATP1B), 25 micrograms of rosuvastatin (BRCP, OATP, and P-gp), and 50 micrograms of atorvastatin (OATP, BCRP, P-gp, and CYP3A4). The DDI studies found that the cocktail had the same effect as the index drugs in earlier trials; however, when employing microdosing, dabigatran etexilate significantly differed from clinical doses, leading to an oral exposure that was about twice as low when dose-normalized and larger interactions [89-90].

Endogenous substrates

It may be more practical to use an endogenous molecule as a measure of the system's activity rather than index substrate medicines to evaluate the offender's effect on a specific pharmacokinetic pathway. A detailed evaluation of the current state, constraints, and methodologies for investigating new endogenous biomarkers for use in DDI investigations has been conducted recently. This method's key benefit is that the index substrate requires no further intervention. This method can be particularly beneficial when the culprit is not safe to administer to healthy volunteers or when the medicine is still in its early stages of clinical research. This role requires the endogenous biomarker to be validated, specific for the enzyme or transporter being studied, and independent of both diet and sickness. Unfortunately, conventional DDI research still hasn't found a suitable replacement for endogenous biomarkers. For example, we could gauge cytochrome 3A activity with 4-hydroxycholesterol, 6-hydroxycortisol, and 6-hydroxycortisone; identify UGT1A1 no selectively with unconjugated bilirubin; and characterize OATP1B1/1B3 with coproporphyrin; however, these methods may only be applicable for preliminary DDI risk assessment [91].

Table4: Examples of drug-dependent infections (DDIs) employing enzymes other than Cytochrome

The enzyme	The victim	The offender (the stopper)	Consequence
Acylpeptidehydrolase	Valproicacidglucuronide	Carbapenems,e.g., meropenem	Decreasedserumvalproicac
COMT	Levodopa	Entacapone	AUC1.5-fold
DPD	5-fluorouracil	Sorivudine	Fluoropyrimidinetoxicity
Monoamineoxidases (AandB)	Dopamine	Moclobemide	Increaseddopamineeffects
Thymidinephosphorylase	Trifluridine	Tipiracil	AUC37-fold
UGT1A1	SN-38(irinotecanactive metabolite)	Lopinavir-ritonavir	AUC3-fold
UGT1A9	Dapagliflozin	Mefenamicacid	AUC1.5-fold
UGT2B7	Lamotrigine	Valproicacid	AUCupto2-fold
Xanthine oxidase	6-mercaptopurine	Allopurinol	AUC5-fold

uridine 5′-diphosphate glucuronosyltransferase (UGT), dihydropyridine dehydrogenase (DPD), DDI, cytochrome P450 (CYP), and catechol-O-methyltransferase (COMT) are all enzymes involved in drug-drug interactions.

Strategies for collecting a limited amount of data and using population pharmacokinetic modeling

To ensure that the extrapolated portion of the overall AUC is less than 20%, it is necessary to thoroughly describe the victim drug's pharmacokinetic profile in stand-alone DDI research using an appropriately frequent and lengthy sampling regimen. Unlike research with healthy volunteers, large patient populations often do not lend themselves to rich sampling strategies. However, in situations where sampling is limited or scarce, population pharmacokinetic studies can aid in understanding the impact of concurrent drugs on the drug of interest. One advantage of these kinds of studies is that they allow researchers to examine DDIs in a clinically relevant population using average doses over an extended period of time. Another benefit is that they can study the effects of commonly prescribed medications without assuming anything about the mechanisms by which they work. To maximize the utility of population pharmacokinetic data, meticulously establish the research methodology, including the sampling technique, prior to starting data collection. Particularly important is the precise recording of medication delivery times and dosages, as well as sample intervals. This will greatly benefit drugs with a short half-lives and variable absorption rates. We should ideally use accessible samples to document the perpetrator's drug exposure. Methods and designs of DDI studies using population pharmacokinetic analysis are discussed in a recent comment made by the International Society of Pharmacometrics Working Group. Population pharmacokinetic studies, as shown in a simulated case study using methotrexate and trastuzumab, may serve as a viable substitute for DDI. Research if they are carefully planned.For pharmaceuticals that serve as index substrates, restricted sampling is also an option as the recognized methods of assessing enzyme activity rely on a metabolic ratio computed from the parent drug and its metabolite. Only the enzyme in issue can produce this ratio, which is and depends on a few or a single sample time point. Exercise caution when interpreting these indicators, particularly if the culprits have the potential to change the fate of the metabolite. In a perfect world with a completely unique index ratio, a metabolic ratio drops of 80% would cause the AUC of a sensitive substrate drug to rise by no more than five times. For instance, delays in medication absorption can introduce substantial variability into restricted sampling methods, especially when metrics rely solely on parent drug concentrations. For midazolam and warfarin, for instance, restricted sample methodologies have shown a weak relationship with comprehensive pharmacokinetic profiles. However, a more practical measure that more precisely represents the drug's systemic clearance is the metabolic ratio, which can be calculated from a single time point. One measure that exemplifies this is paraxanthine, the product of the selective metabolism of caffeine by CYP1A2. One way to measure CYP1A2 activity is to measure the ratio of paraxanthine to caffeine in a single plasma sample that was obtained four to six hours after caffeine consumption. Researchers have also investigated the use of such one-time metabolic ratios in index medication combinations. Unfortunately, cocktail methods only allow for one sample period, which is may not be perfect for every index substrate, but it is a compromise between them all. One approach to decrease blood sample sizes and make blood collection more practicable is to use dried blood as the sample matrix in combination with capillary blood microsamples. Among the many possible advantages of this approach are its versatility and low level of intrusiveness, which might make it applicable in contexts with little resources or even motivate participants to self-sample. Verifying venipuncture samples used to measure whole blood concentrations in this matrix is required since drug concentrations in plasma/serum and whole blood are not always the same. While large-scale research using dried blood samples is useful, such as phase III trials or studies involving sensitive populations like children, they are not particularly applicable to formal DDI investigations conducted on healthy participants. Restricted sampling tactics make this especially true [92-95].

Physiologically-based pharmacokinetic modeling

Evidenced by data on CYP decrease in a controlled laboratory context, there has been significant advancement in the modelling methodologies used to anticipate DDIs during the previous 20 years. Decisions made by regulators are also increasingly using physiologically-based pharmacokinetic models. which are PBPK models. It is a fluid approach that takes into consideration the fact that drug concentrations could alter over time. Pharmacokinetics (PBPK) models the drug's concentration-time profile in plasma and/or target organ models make it possible to model multiple drug disposition processes at once., offering a variety of options. As clinical data and understanding of the medication and its metabolite disposition/elimination routes increase, so does the credibility of PBPK models. Ideally, the model may be cross-validated with information from many clinical trials including the offender and the medication used by the victim [96].

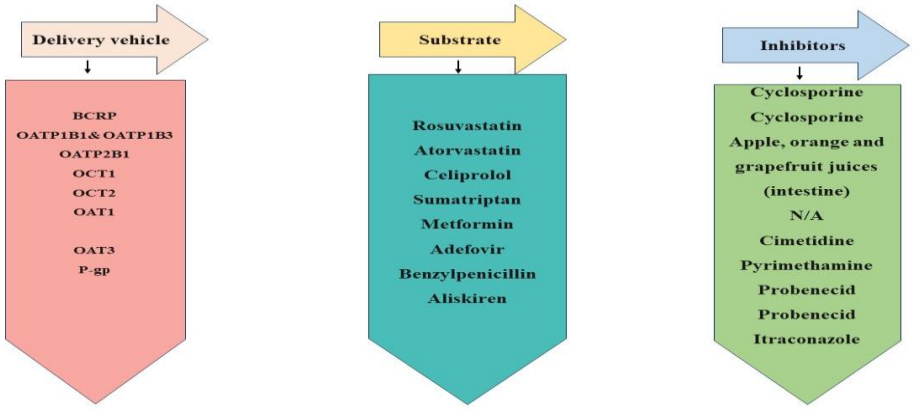

Figure 2: Clinical DDI study substrates and inhibitors for transporter probes [6]

For the purpose of DDI prediction, the pharmaceutical sector is using PBPK models at a rising rate. associated dose choices as a means of replacing drugs for clinical research, and regulatory bodies are also encouraging this practice. 8 Submittals for cobimetinib, lesinurad, and olaparib, among others, have included PBPK DDI simulations in lieu of clinical DDI investigations. One use of PBPK DDI modelling in regulatory submissions is to (i) anticipate DDIs using medications that aren't utilized in clinical research for both the offender and the victim; (ii) look forward to DDIs in various subpopulations, including groups with varying hereditary CYP activity or populations comprising particular patients; (iii) foretell the outcomes of various dose plans or administrations of the offender's or victim's medication; (iv) foretell how changing the pH will influence the diffusion and solubility of drugs; and (v) determine how certain drug enzymes and transporters will react to an offending substance. On top of that, PBPK DDI modelling has been essential in the development of clinical DDI research and the mechanical explanation of DDIs seen in clinical settings.When the interaction depends on reversible CYP inhibition, several PBPK DDI models have been successful. However, when time-dependent inhibition is combined with other, less well-established processes, including reversible inhibition or induction, the resulting effects are less amenable to modelling. Uncertainty regarding the expression levels and turnover characteristics of transporters and enzymes, a dearth of specific in vivo data, and the scaling of drug concentration levels at the correct cellular or subcellular sites all make it difficult to model DDIs that affect non-CYP drug-metabolizing enzymes and drug transporters. Drug influx to hepatocytes mediated by OATP1B1 is a nice example of a transporter-DDI that is difficult to describe.Because the in vitro OATP1B1 Ki values of clarithromycin, cyclosporine, rifampin, and clopidogrel acyl-β-D glucuronide do not seem to be low enough, modelers have had to adjust the OATP1B1 inhibition constant values in PBPK models based on measured values in order to account for drug-dose interactions (DDIs) observed in clinical trials. It is possible that this departure from physiological principles is caused by the interaction between drug transporters and drug-metabolizing enzymes, together with the time-dependent inhibition of OATP1B1 by these inhibitors. Our current knowledge of the biochemical and physiological processes linked to transporter-mediated DDIs is severely lacking, which is a big problem when trying to build PBPK models or make in vitro-in vivo predictions in general.

Taken together, PBPK modelling and clinical DDI investigations are powerful resources for the field of DDI research. Nevertheless, it is important to consider the current limits of PBPK modelling in complicated scenarios, including numerous processes and DDIs. Overall, model creation and quality assessment methods have been inconsistent, highlighting the need for best-practice recommendations and the harmonization of regulations across regulatory bodies. Still, PBPK models have great potential for use in the future when it comes to designing and organizing more clinical trials, as well as in interpreting and applying results from clinical DDI investigations to new contexts [96].

COMPLEX DDIS

While DDIs derived from a single well-established pharmacokinetic mechanism may be confidently anticipated and used in many clinical settings, the complexity the mechanics of pharmacokinetic interactions is become clearer. During the first phases of medication discovery, complex Predicting and managing DDIs may be difficult. Autoinhibition or induction of the drug's own metabolism, time-dependent inhibition, inhibition or induction by major drug metabolites, the possibility of multiple concurrent mechanisms, and many more such mechanisms are among the most problematic and complex in drug development and clinical practice. Even if comprehensive preclinical data is available, understanding the clinical relevance of DDIs requires clinical DDI research. and modeling methodologies are fundamental for comprehending them. Example: current preclinical research methods allow for early suspicion of autoinduction and autoinhibition; nevertheless, the clinical relevance of these effects is only shown by the first clinical pharmacokinetic investigations. At its worst, autoinduction may be so powerful that no amount of medication exposure is ever enough to pass the drug development program's muster. Conversely, the drug's sensitivity to inhibitory perpetrators may be altered by autoinduction or autoinhibition, which in turn can cause changes in the relative importance of distinct disposition routes that are dose-and time-dependent. One example is imatinib, a tyrosine kinase inhibitor that increases plasma concentrations of simvastatin and other CYP3A4 substrates by inhibiting CYP3A4. Due to the importance of CYP3A4 in imatinib metabolism, inhibitors of this enzyme can cause the alternative elimination pathway (CYP2C8) to become more important, which in turn increases the risk of elevated When taking numerous doses of imatinib, the levels of the drug might be affected by CYP2C8 inhibitors. The CYP3A4 substrate, inhibitor, and inducer are shown in Figure 3. the kinase inhibitor midostaurin, an even more complicated medication. Theoretically, midostaurin may first induce a transient net suppression of CYP3A4, which might later change into a temporary net induction. A quick analysis using midazolam as the victim drug suggests that the effect of midostaurin on CYP3A4 could have been negligible. It is unclear if midostaurin acts as an inducer to lower CYP3A4 substrate concentrations throughout long-term treatment, and DDI studies performed at two early time points may not have shown a transitory inhibition at treatment initiation. Another thing to think about is that the true sensitivity of single-dose midostaurin to CYP3A4 inhibition may not have been shown at steady state, when auto-induction has increased CYP3A4's metabolic function. To unravel this kind of dose- and time-dependent intricacy, clinical DDI research must include the drug as both an offender and a victim. In addition, it is necessary to conduct clinical DDI studies at various points throughout treatment because PBPK models do not work well in this domain. This is especially true when it comes to DDIs involving drugs with nonlinear pharmacokinetics, where there is a lack of data on the dose and time dependency of these injections, and when it comes to the enzyme-specificity of induction, which is not well understood. Several DDIs, such gemfibrozil-repaglinide, cyclosporine-rosuvastatin, sofosbuvir/velpatasvir/voxilaprevir-rosuvastatin, and others that inhibit oATP1B1/1B3 and CYP2C8, OATP1B, and BCRP, respectively OATP1B1/1B3 and BCRP), and many ritonavir-victim drugs (which inhibit P-gp and CYP3A4 and induce CYP), are examples of Directed disintegration incidents (DDIs) using several processes. To further understand this kind of DDI risk, researchers should look at preclinical and clinical trials that specifically target enzymes and transporters to see which ones are involved in the drug's metabolism and disposal. ones the medicine inhibits or promotes. Then, relevant DDIs with the potential for numerous routes may be studied simultaneously in a clinical

context using standard procedures. If further mechanistic information is needed, it might be advantageous to do experiments with different inhibitor doses or timings, or trials with more than one offender. It is common practice to thoroughly do in vitro research to first identify risks related to complex DDIs, such as those caused by inhibitory or boosting primary metabolites or mechanism-based inhibition. The metabolites' involvement as offenders has just been recognized in the last decade. The clinically observed suppression of CYP2C9, CYP2D6, and CYP3A4 can only be explained by the inhibitory metabolites of amiodarone, bupropion, and sertraline, respectively. Notably, even glucuronide metabolites may block CYP enzymes via mechanism-based inhibition, which can lead to severe DDIs. Standard procedures for investigating DDIs in healthcare settings are usually applicable. Nevertheless, in order to determine the time-dependence of the DDI risk, focused study or long-term administration of metabolites with a very long half-life (t1/2) may be necessary. An increasing number of newly launched pharmaceuticals, especially antiviral agents, are fixed-dose combination medicines, which further complicates the already challenging task of understanding the role of each pharmacological component in the overall clinical impact when the combination is examined as a whole. When many harmful medications are present simultaneously or when genetic variations or disease conditions affect the probability of DDIs76, for example, clinical concerns usually need DDI-specific study. The pharmacokinetics of loperamide and repaglinide might be significantly affected by the concurrent use of gemfibrozil and itraconazole, two medications that are substrates for the CYP2C8 and CYP3A4 enzymes, respectively.Due to genetic variations, weak metabolizers may be more susceptible to drug-induced diarrhea (DDIs) caused by medications that inhibit a different pathway, such as CYP3A4. However, these individuals may not respond favorably to medications that inhibit the enzyme responsible for the deficiency, such as omeprazole or paroxetine, which block CYP2D6 and CYP2C19, respectively. When it comes to genetic differences that lead to a rise in activity, the usual rule is the inverse. The level of inhibition or induction, however, might alter depending on the quantity of perpetra-tor medicine, which can be influenced by differences in genes. As an example, voriconazole is a CYP2C19 substrate. For Theophylline oral clearance was 62% decreased in healthy subjects by fluvoxamine, whereas it was only 12% reduced in individuals with severe cirrhosis. These patients may not be at risk of contracting this DDI. Conducted research studies It is the victim drug's characteristics, including its essential enzymes and transporters, that dictate the kind of complex DDI that will be used. Larger clinical studies with sufficient patients in each genotype or disease group are often required for such investigations to investigate several culprits or combinations of offenders., or a multiphase crossover study. Although the research designs are simple, recruiting enough people with unusual genotypes or rare diseases might be difficult[95].

PITFALLS AND INTERPRETATION OF DDI STUDIES

Pitfalls

Ethical concerns, false alarms, or, worst case scenario, the inability to identify pertinent DDI dangers could result from erroneous results, DDI study design, and implementation (Table 1). Due to limitations in preclinical research and a lack of understanding of certain pharmacokinetic pathways, it has been very difficult to identify clinically hazardous DDIs. People didn't comprehend the victim pharmaceuticals' toxicity based on dosage and fundamental mechanistic difficulties, therefore the market pulled cerivastatin, cisapride, and terfenadine from circulation while Sorivudine was the villain. Although this is not an exhaustive list of possible issues, we will discuss three instances when assuming the incorrect thing about the DDI risk led to difficulties.The late 1990s saw the beginning of CYP2C8's comprehensive understanding of its function in medication metabolism. Learning how this DDI functioned required extensive in vitro and clinical research. Gemfibrozil and cerivastatin's combination demonstrated the enzyme's potential importance. One of the initial justifications for bringing cerivastatin to market was the belief that the drug's metabolism by CYP3A4 and CYP2C8 would provide advantageous interaction potential. The product was pulled off sale in 2001 due to many instances of rhabdomyolysis. Almost half of the cases were individuals who were taking both gemfibrozil and cerivastatin simultaneously, which regrettably led to a number of deaths. The AUC of cerivastatin was enhanced by a factor of five to six due to gemfibrozil's substantial reduction of its CYP2C8-dependent M-23 metabolite, while itraconazole's little impact on cerivastatin exposure was due to its strong CYP3A4 suppression. At first, gemfibrozil was shown to inhibit CYP2C8 weakly and nonselectively in vitro. It wasn't until much later that the process by which 1-O-glucuronide, the active metabolite of gemfibrozil, inhibited CYP2C8 was uncovered. This case demonstrated the practical difficulty of DDI prediction without thorough investigation and understanding of the DDI features of the medications used by the victim and the perpetrator.Initially, rofecoxib was believed to be a weak CYP1A2 inhibitor; it is a nonsteroidal anti-inflammatory drug that specifically inhibits cyclooxygenase-2.A double-blind experiment using theophylline as the CYP1A2 index substrate provides the majority of the labeling information. In this research, the only way to increase theophylline's AUC by 1.5 times was to take 25 mg of rofecoxib one day. Still, rofecoxib induces a 13.6-fold increase in AUC due to its significant blocking of CYP1A2 in DDI tests using tizanidine as the probe substrate. 88 Theophylline is not a sensitive in vivo index substrate of CYP1A2 owing to its high bioavailability and lack of first-pass metabolism. This exacerbates the perception of unbalance. In vitro proof of rofecoxib's efficacy as a mechanism-based CYP1A2 inhibitor did not become available for quite some time.The inhibitor dose and the substrate's timing relative to inhibitor administration may affect the observed interaction to a substantial extent. One example is the study of the interactions between the intestinal CYP3A inhibitor grapefruit juice and the enzyme substrate lovastatin. In their experiment, Rogers et al. gave participants 90 millilitres of grapefruit juice four times a day first thing in the morning and 40 milligrams of lovastatin at night on day three. The AUC of lovastatin was 1.9 times raised by grapefruit juice, despite the fact that the AUC of lovastatin acid was only 1.6 times increased. The report is missing information on how often the victim and offender were dosed. Previous research by Kantola et al., found that lovastatin and lovastatin acid both had their AUC values enhanced by grape-fruit juice, with the former increasing them by 15-fold and the latter by 5-fold. However, our findings disprove that finding. Subjects in this study were given grapefruit juice three times daily for the first two days, lovastatin simultaneously on the third day, and further grapefruit juice thirty minutes and sixty minutes following the lovastatin. Although this amount of juice is very

improbable in actual use, the data does point to a possible worst-case scenario regarding the interaction between grapefruit juice and lovastatin. A DDI investigation isn't complete without considering the research design in before, throughout, and after the process, as this case study shows[96].If you follow the rules, you should be able to avoid the worst issues as the regulatory bodies have updated the DDI recommendations on a regular basis during the past 20 years. Research into transporters and metabolisms that are not mediated by CYP enzymes is continuing, which will improve the methodology of DDI investigations and make DDIs more predictable. The quantitative participation of all key drug disposal mechanisms cannot be assessed solely from in vitro data. Therefore, it is a risky error to rely on PBPK modelling in cases when its accuracy is debatable due to a lack of further clinical data, such in the case of complicated DDIs (as mentioned above) [97].

Analysis and generalization of results

You can easily interpret findings from standard DDI experiments using identify substrates or inhibitors of pathways to classify the tested drug's efficacy as an inducer or inhibitor of a transporter or enzyme. Considerations for DDI result interpretation include the selectivity and potency of the index perpetrator at the specified dosage, the sensitivity of the index substrate, and the study's general design, which incorporates dose and temporal links. While a persist or medicine may block a single metabolic pathway, its efficacy as an inhibitor will be diminished if the index drug has sufficient sensitivity.Applying the findings to other contexts and making sense of complex events may be made much easier using the PBPK paradigm. It is important to proceed with caution when extrapolating findings from the DDI to different dose scenarios or drugs when transporters, metabolism, induction, and inhibition are all working together. If one mechanism is significant (like CYP3A4 inhibition), then findings may be extrapolated to other contexts with more certainty. However, it's worth mentioning that a highly sensitive but nonselective index substrate, which is the product of metabolism and transport collaborating, may be better than a weakly sensitive index substrate when trying to determine DDI risk. But there are a lot of complicated factors to consider when figuring out the DDI's therapeutic relevance. Time- and dose-dependent pharmacokinetics of the victim medication, various methods of transporter and enzyme inhibition and induction occurring simultaneously, etc. Midostaurin and imatinib are two examples of victim drugs whose DDI sensitivity might shift due to time-dependent alterations in their pharmacokinetics. The amount of DDIs that occur during the victim's absorption and first-pass metabolism (e.g., using PBPK modeling) may be affected by the interpretation should take into account the dosage delay between the perpetrator and the victim [39].

CONCLUSION

Medication safety evaluations must include the DDI potential of both existing and future drugs. Recent advances in in vitro research and modeling approaches have greatly expanded our understanding Modeling and in vitro research have recently made tremendous strides, significantly of the molecular mechanisms involved in DDIs, as well as our ability to anticipate and interpret them. However, when it comes to determining the hazards of DDIs, clinical DDI investigations are still essential. Additional research, including as in vitro reverse translation tests, has validated the findings of earlier studies on clinical DDIs, which have uncovered DDIs that were previously unknown and provided insight into their mechanisms. To fully understand DDIs and their clinical significance, it is recommended to combine in silico models with clinical research that concentrate on DDIs. This is because clinical studies may not account for all the potential permutations of variables that impact the result. In conclusion, there is no optimal method for studying DDIs; however, to guarantee the research's security and maximize its potential, the available data, every study's design should include a comprehensive evaluation of the available data.

REFERENCES-

1. Dechanont, S.; Maphanta, S.; Butthum, B.; Kongkaew, C. Hospital admissions/visits associated with drug–drug interactions: a systematic review and meta-analysis. Pharmacoepidemiology and Drug Safety 2014, 23 (5), 489–497. https://doi.org/10.1002/pds.3592.
2. Orlando, R.; Padrini, R.; Perazzi, M.; Demartin, S.; Piccoli, P.; Palatini, P. Liver dysfunction markedly decreases the inhibition of cytochrome P450 1A2–mediated theophylline metabolism by fluvoxamine. *Clinical Pharmacology & Therapeutics* 2006, *79* (5), 489–499. https://doi.org/10.1016/j.clpt.2006.01.012.
3. Onakpoya, I. J.; Heneghan, C. J.; Aronson, J. K. Delays in the post-marketing withdrawal of drugs to which deaths have been attributed: a systematic investigation and analysis. *BMC Medicine* 2015, *13* (1). https://doi.org/10.1186/s12916-014-0262-7.
4. Yu, J.; Petrie, I. D.; Levy, R. H.; Ragueneau-Majlessi, I. Mechanisms and Clinical Significance of Pharmacokinetic-Based Drug-Drug Interactions with Drugs Approved by the U.S. Food and Drug Administration in 2017. Drug Metabolism and Disposition 2018, 47 (2), 135–144. https://doi.org/10.1124/dmd.118.084905.
5. Backman, J. T.; Kivistö, K. T.; Olkkola, K. T.; Neuvonen, P. J. The area under the plasma concentration-time curve for oral midazolam is 400-fold larger during treatment with itraconazole than with rifampicin. *European Journal of Clinical Pharmacology* 1998, *54* (1), 53–58. https://doi.org/10.1007/s002280050420.
6. Tornio, A.; Filppula, A. M.; Niemi, M.; Backman, J. T. Clinical Studies on Drug–Drug Interactions Involving Metabolism and Transport: Methodology, Pitfalls, and Interpretation. *Clinical Pharmacology & Therapeutics* 2019, *105* (6), 1345–1361. https://doi.org/10.1002/cpt.1435.
7. De Jong, J.; Skee, D.; Murphy, J.; Sukbuntherng, J.; Hellemans, P.; Smit, J.; De Vries, R.; Jiao, J. J.; Snoeys, J.; Mannaert, E. Effect of CYP 3A perpetrators on ibrutinib exposure in healthy participants. *Pharmacology Research & Perspectives* 2015, *3* (4). https://doi.org/10.1002/prp2.156.
8. Fuhr, U.; Hsin, C.-H.; Li, X.; Jabrane, W.; Sörgel, F. Assessment of Pharmacokinetic Drug–Drug Interactions in Humans: In Vivo Probe Substrates for Drug Metabolism and Drug Transport Revisited. *The Annual Review of Pharmacology and Toxicology* 2019, *59* (1), 507–536. https://doi.org/10.1146/annurev-pharmtox-010818-021909.
9. Grimstein, M.; Yang, Y.; Zhang, X.; Grillo, J.; Huang, S.-M.; Zineh, I.; Wang, Y. Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update From the U.S. Food and Drug Administration's Office of Clinical Pharmacology. *Journal of Pharmaceutical Sciences* 2019, *108* (1), 21–25. https://doi.org/10.1016/j.xphs.2018.10.033.
10. Prueksaritanont, T.; Chu, X.; Gibson, C.; Cui, D.; Yee, K. L.; Ballard, J.; Cabalu, T.; Hochman, J. Drug–Drug Interaction Studies: Regulatory Guidance and An Industry Perspective. *The AAPS Journal* 2013, *15* (3), 629–645. https://doi.org/10.1208/s12248-013-9470-x.
11. Rekić, D.; Reynolds, K. S.; Zhao, P.; Zhang, L.; Yoshida, K.; Sachar, M.; Miller, M. P.; Huang, S.-M.; Zineh, I. Clinical Drug–Drug Interaction Evaluations to Inform Drug Use and Enable Drug Access. *Journal of Pharmaceutical Sciences* 2017, *106* (9), 2214–2218. https://doi.org/10.1016/j.xphs.2017.04.016.
12. Tornio, A.; Filppula, A. M.; Kailari, O.; Neuvonen, M.; Nyrönen, T. H.; Tapaninen, T.; Neuvonen, P. J.; Niemi, M.; Backman, J. T. Glucuronidation Converts Clopidogrel to a Strong Time-Dependent Inhibitor of CYP2C8: A Phase II Metabolite as a Perpetrator of Drug–

Drug Interactions. *Clinical Pharmacology & Therapeutics* 2014, *96* (4), 498–507. https://doi.org/10.1038/clpt.2014.141.

13. Niemi, M.; Backman, J. T.; Fromm, M. F.; Neuvonen, P. J.; Kivistö, K. T. Pharmacokinetic Interactions with Rifampicin. *Clinical Pharmacokinetics* 2003, *42* (9), 819–850. https://doi.org/10.2165/00003088-200342090-00003.

14. Backman, J.; Luurila, H.; Neuvonen, M.; Neuvonen, P. Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. Clinical Pharmacology & Therapeutics 2005, 78 (2), 154–167. https://doi.org/10.1016/j.clpt.2005.04.007.

15. Lau, Y. Y.; Huang, Y.; Frassetto, L.; Benet, L. Z. Effect of OATP1B Transporter Inhibition on the Pharmacokinetics of Atorvastatin in Healthy Volunteers. Clinical Pharmacology & Therapeutics 2006, 81 (2), 194–204. https://doi.org/10.1038/sj.clpt.6100038.

16. Niemi, M.; Pasanen, M. K.; Neuvonen, P. J. Organic Anion Transporting Polypeptide 1B1: a Genetically Polymorphic Transporter of Major Importance for Hepatic Drug Uptake. Pharmacological Reviews 2011, 63 (1), 157–181. https://doi.org/10.1124/pr.110.002857.

17. Hukkanen, J. Induction of cytochrome P450 enzymes: a view on humanin vivofindings. *Expert Review of Clinical Pharmacology* 2012, *5* (5), 569–585. https://doi.org/10.1586/ecp.12.39.

18. Zamek-Gliszczynski, M. J.; Taub, M. E.; Chothe, P. P.; Chu, X.; Giacomini, K. M.; Kim, R. B.; Ray, A. S.; Stocker, S. L.; Unadkat, J. D.; Wittwer, M. B.; Xia, C.; Yee, S.; Zhang, L.; Zhang, Y. Transporters in Drug Development: 2018 ITC Recommendations for Transporters of Emerging Clinical Importance. *Clinical Pharmacology & Therapeutics* 2018, *104* (5), 890–899. https://doi.org/10.1002/cpt.1112.

19. Giacomini, K. M.; Huang, S.-M.; Tweedie, D. J.; Benet, L. Z.; Brouwer, K. L. R.; Chu, X.; Dahlin, A.; Evers, R.; Fischer, V.; Hillgren, K. M.; Hoffmaster, K. A.; Ishikawa, T.; Keppler, D.; Kim, R. B.; Lee, C. A.; Niemi, M.; Polli, J. W.; Sugiyama, Y.; Swaan, P. W.; Ware, J. A.; Wright, S. H.; Yee, S. W.; Zamek-Gliszczynski, M. J.; Zhang, L. Membrane transporters in drug development. *Nature Reviews Drug Discovery* 2010, *9* (3), 215–236. https://doi.org/10.1038/nrd3028.

20. Elsby, R.; Martin, P.; Surry, D.; Sharma, P.; Fenner, K. Solitary Inhibition of the Breast Cancer Resistance Protein Efflux Transporter Results in a Clinically Significant Drug-Drug Interaction with Rosuvastatin by Causing up to a 2-Fold Increase in Statin Exposure. *Drug Metabolism and Disposition* 2015, *44* (3), 398–408. https://doi.org/10.1124/dmd.115.066795.

21. Lund, M.; Petersen, T. S.; Dalhoff, K. P. Clinical Implications of P-Glycoprotein Modulation in Drug–Drug Interactions. *Drugs* 2017, *77* (8), 859–883. https://doi.org/10.1007/s40265-017-0729-x.

22. Jalava, K.-M.; Partanen, J.; Neuvonen, P. J. Itraconazole Decreases Renal Clearance of Digoxin. Therapeutic Drug Monitoring 1997, 19 (6), 609–613. https://doi.org/10.1097/00007691-199712000-00001.

23. Stopfer, P.; Giessmann, T.; Hohl, K.; Sharma, A.; Ishiguro, N.; Taub, M.; Zimdahl-Gelling, H.; Gansser, D.; Wein, M.; Ebner, T.; Müller, F. Pharmacokinetic Evaluation of a Drug Transporter Cocktail Consisting of Digoxin, Furosemide, Metformin, and Rosuvastatin. Clinical Pharmacology & Therapeutics 2016, 100 (3), 259–267. https://doi.org/10.1002/cpt.406.

24. Chu, X.; Liao, M.; Shen, H.; Yoshida, K.; Zur, A. A.; Arya, V.; Galetin, A.; Giacomini, K. M.; Hanna, I.; Kusuhara, H.; Lai, Y.; Rodrigues, D.; Sugiyama, Y.; Zamek-Gliszczynski, M. J.; Zhang, L. Clinical Probes and Endogenous Biomarkers as Substrates for Transporter Drug-Drug Interaction Evaluation: Perspectives From the International Transporter Consortium. Clinical Pharmacology & Therapeutics 2018, 104 (5), 836–864. https://doi.org/10.1002/cpt.1216.

25. Zamek-Gliszczynski, M. J.; Chu, X.; Cook, J. A.; Custodio, J. M.; Galetin, A.; Giacomini, K. M.; Lee, C. A.; Paine, M. F.; Ray, A. S.; Ware, J. A.; Wittwer, M. B.; Zhang, L. ITC Commentary on Metformin Clinical Drug–Drug Interaction Study Design That Enables an Efficacy- and Safety-Based Dose Adjustment Decision. Clinical Pharmacology & Therapeutics 2018, 104 (5), 781–784. https://doi.org/10.1002/cpt.1082.

26. Guo, Y.; Chu, X.; Parrott, N. J.; Brouwer, K. L. R.; Hsu, V.; Nagar, S.; Matsson, P.; Sharma, P.; Snoeys, J.; Sugiyama, Y.; Tatosian, D.; Unadkat, J. D.; Huang, S.; Galetin, A. Advancing Predictions of Tissue and Intracellular Drug Concentrations Using In Vitro, Imaging and Physiologically Based Pharmacokinetic Modeling Approaches. Clinical Pharmacology & Therapeutics 2018, 104 (5), 865–889. https://doi.org/10.1002/cpt.1183.

27. Kajosaari, L. I.; Niemi, M.; Neuvonen, M.; Laitila, J.; Neuvonen, P. J.; Backman, J. T. Cyclosporine markedly raises the plasma concentrations of repaglinide. Clinical Pharmacology & Therapeutics 2005, 78 (4), 388–399. https://doi.org/10.1016/j.clpt.2005.07.005.

28. Kajosaari, L. I.; Niemi, M.; Neuvonen, M.; Laitila, J.; Neuvonen, P. J.; Backman, J. T. Cyclosporine markedly raises the plasma concentrations of repaglinide. *Clinical Pharmacology & Therapeutics* 2005, *78* (4), 388–399. https://doi.org/10.1016/j.clpt.2005.07.005.

29. Yee, S. W.; Brackman, D. J.; Ennis, E. A.; Sugiyama, Y.; Kamdem, L. K.; Blanchard, R.; Galetin, A.; Zhang, L.; Giacomini, K. M. Influence of Transporter Polymorphisms on Drug Disposition and Response: A Perspective From the International Transporter Consortium. Clinical Pharmacology & Therapeutics 2018, 104 (5), 803–817. https://doi.org/10.1002/cpt.1098.

30. Bank, P.; Caudle, K.; Swen, J.; Gammal, R.; Whirl-Carrillo, M.; Klein, T.; Relling, M.; Guchelaar, H. Comparison of the Guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group. Clinical Pharmacology & Therapeutics 2017, 103 (4), 599–618. https://doi.org/10.1002/cpt.762

31. Fuhr, U.; Jetter, A.; Kirchheiner, J. Appropriate Phenotyping Procedures for Drug Metabolizing Enzymes and Transporters in Humans and Their Simultaneous Use in the "Cocktail" Approach. Clinical Pharmacology & Therapeutics 2007, 81 (2), 270–283. https://doi.org/10.1038/sj.clpt.6100050.

32. Mikus, G. Probes and Cocktails for Drug–Drug Interaction Evaluation: The Future Is Microdosing? Clinical Pharmacology & Therapeutics 2019, 105 (6), 1335–1337. https://doi.org/10.1002/cpt.1350.

33. Bosilkovska, M.; Samer, C. F.; Déglon, J.; Rebsamen, M.; Staub, C.; Dayer, P.; Walder, B.; Desmeules, J. A.; Daali, Y. Geneva Cocktail for Cytochrome P450 and P-Glycoprotein Activity Assessment Using Dried Blood Spots. Clinical Pharmacology & Therapeutics 2014, 96 (3), 349–359. https://doi.org/10.1038/clpt.2014.83.

34. Derungs, A.; Donzelli, M.; Berger, B.; Noppen, C.; Krähenbühl, S.; Haschke, M. Effects of Cytochrome P450 Inhibition and Induction on the Phenotyping Metrics of the Basel Cocktail: A Randomized Crossover Study. Clinical Pharmacokinetics 2015, 55 (1), 79–91. https://doi.org/10.1007/s40262-015-0294-y.

35. Stopfer, P.; Giessmann, T.; Hohl, K.; Sharma, A.; Ishiguro, N.; Taub, M.; Zimdahl-Gelling, H.; Gansser, D.; Wein, M.; Ebner, T.; Müller, F. Pharmacokinetic Evaluation of a Drug Transporter Cocktail Consisting of Digoxin, Furosemide, Metformin, and Rosuvastatin. *Clinical Pharmacology & Therapeutics* 2016, *100* (3), 259–267. https://doi.org/10.1002/cpt.406.

36. Stopfer, P.; Giessmann, T.; Hohl, K.; Sharma, A.; Ishiguro, N.; Taub, M. E.; Jungnik, A.; Gansser, D.; Ebner, T.; Müller, F. Effects of Metformin and Furosemide on Rosuvastatin Pharmacokinetics in Healthy Volunteers: Implications for Their Use as Probe Drugs in a Transporter Cocktail. European Journal of Drug Metabolism and Pharmacokinetics 2017, 43 (1), 69–80. https://doi.org/10.1007/s13318-017-0427-9.

37. Prueksaritanont, T.; Tatosian, D.; Chu, X.; Railkar, R.; Evers, R.; Chavez-Eng, C.; Lutz, R.; Zeng, W.; Yabut, J.; Chan, G.; Cai, X.; Latham, A.; Hehman, J.; Stypinski, D.; Brejda, J.; Zhou, C.; Thornton, B.; Bateman, K.; Fraser, I.; Stoch, S. Validation of a microdose probe drug cocktail for clinical drug interaction assessments for drug transporters and CYP3A. Clinical Pharmacology & Therapeutics 2016, 101 (4), 519–530. https://doi.org/10.1002/cpt.525.

38. Chu, X.; Chan, G. H.; Evers, R. Identification of Endogenous Biomarkers to Predict the Propensity of Drug Candidates to Cause Hepatic or Renal Transporter-Mediated Drug-Drug Interactions. Journal of Pharmaceutical Sciences 2017, 106 (9), 2357–2367https://doi.org/10.1016/j.xphs.2017.04.007.

39. Mariappan, T. T.; Shen, H.; Marathe, P. Endogenous Biomarkers to Assess Drug-Drug Interactions by Drug Transporters and Enzymes. Current Drug Metabolism 2017, 18 (8). https://doi.org/10.2174/1389200218666170724110818.

40. Arora S, Dubey A, Kumari M. The role of 3- D printing technologies. Int J Pharm Chem Anal 2024;11(2):112-120.https://doi.org/10.18231/j.ijpca.2024.016.

41. Kumari, M., Shukla, D., Das, S.S., Dubey, A., Tiwari, A., and Sonker, A. (2024). Larvicidal Efficacy of Alcohol-Based Extraction of Vernonia Amygdalina with Bacillus Thuringiensis on the Vector Aedes Aegypti. ShodhKosh: Journal of Visual and Performing Arts, 5(7), 88–93. doi: 10.29121/shodhkosh.v5.i7.2024.1982

42. Anubhav Dubey, Mamta Kumari, Vimal Kumar. In vivo antidiabetic activity of asparagus racemosus seeds in streptozotocin induced diabetic model. May-June 2024, V2 – I3, Pages - 0146 – 0152. Doi: https://doi.org/10.55522/ijti.V2I3.0037.

43. Sharma, D.; Ruhil, B.; **Dubey, A.**; Jain, D.; Bhatia, D.; Koubouris, G. Unlocking Rapid and User-Friendly Strategies to Improve Horticultural Crop Qualities. Horticulturae 2024, 10, 779.https://doi.org/10.3390/horticulturae10080779.

44. Dubey, A., Ansari M.V.,Sahu, V. K., Mishra A. Assessment of in-vitro Antimicrobial and Antioxidant Activity of Essential oil obtained from *Artemisia Argyi*. (2024). *Cahiers Magellanes*-NS, 6(2),2961-2975. https://magellanes.com/index.php/CMN/article/view/554.

45. Anubhav Dubey, Mamta Kumari, Vimal Kumar. Formulation and Evaluation of Antiviral Agent Loaded Polymeric Nanoparticles. May-June 2024, V2 – I3, Pages - 0163 – 0169. Doi: https://doi.org/10.55522/ijti.V2I3.0052.

46. Dubey, A., Kumari M., Sahu, V. K., Mishra, A Dash, S. L., &. (2024). Zebrafish as a fascinating animal model: a robust platform for in vivo screening for biomedical researches. International Journal of Agricultural Sciences and Veterinary Medicine, 12(1), 173–187. https://doi.org/10.25303/1201ijasvm034039

47. Dubey A, Samra, Sahu VK, Dash SL and Mishra A: A review on plant Opiliaceltidifolia: an assessment of its botany, conventional utilization, phytochemistry and pharmacology. Int J Pharm Sci & Res 2024; 15(3): 690-98. doi: 10.13040/IJPSR.0975-8232.15(3).690-98.

48. Anubhav Dubey, Shilpi arora, Swikriti Sharma, Gurpreet Kaur, Vaishali Goel, Meenakshi Ghildiyal, & Mamta Kumari. (2024). A Systemic Education of Therapeutic Approaches Using Native Herbs to Treat Rheumatoid Joint Dysfunction. Educational Administration: Theory and Practice, 30(5), 67–83. https://doi.org/10.53555/kuey.v30i4.2774

49. Dubey, A., Kumari M., Pandey M., (2024). Homeopathic Medicinal Products and Importance in Diabetes *International Journal of Homeopathy & Natural Medicines*. 10(1), 17–26. https://doi.org/10.11648/j.ijhnm.20241001.12

50. Dwivedi S., Chandekar A., Tripathi A., Mishra R., Chhajed M., Sharma P.K., Dubey A., (2024). In-Vivo Anti-diabetic activity of Leonotisnepetaefolia (L.) R.Br. Root in Alloxan induced Diabetic Model. Naturalista Campano. 28(1), 2190–93 https://museonaturalistico.it

51. Dubey, A., Ghosh, N. S., Singh, R. (2023). An in-depth and in vitro evaluation of the antioxidant and neuroprotective activity of aqueous and ethanolic extract of Asparagus racemosus Linn seed. Research Journal of Chemistry and Environment. 27 (10), Pages-46-66. https://doi.org/10.25303/2710rjce046066

52. Dubey, A. ., Ghosh, N. S. ., & Singh, R. . (2023). A Toxicological Study on Seed Extracts of Asparagus Racemosus Linn (Ethanolic and Water) in Experimental Animals. Journal of Advanced Zoology, 44(2), 71–78. https://doi.org/10.17762/jaz.v44i2.194

53. Dubey Anubhav, Basak Mrinmoy, Dey Biplab and Ghosh Niladry, (2023). Queen of all herbs (Asparagus racemosus): an assessment of its botany, conventional utilization, phytochemistry and pharmacology. Research Journal of Biotechnology.18(6), Pages- 146-154. https://doi.org/10.25303/1806rjbt1460154.

54. Dubey A, Ghosh NS, Singh Karuna, Verma Princy, (2023).Hematological and hypolipidemic effects of methanol extract of oldenandia corymbose (rubiaceous) seeds in streptozotocin (stz) diabetic in wistar rats A Journal for New Zealand Herpetology,12(3),2203-2210.DOI : http://biogecko.co.nz/.2023.v12.i03.pp2309-2317.

55. Purohit D, Hypolipidemic and haematological effects of ethanolic extract of Tecoma stans linn(bignoniaceae) seeds in alloxan-induced diabetic albino rats. Korean Journal of Physiology and Pharmacology, 2023:27(1),85-90. DOI:10.25463/kjpp.27.1.2023.8.

56. Anubhav Dubey, Niladry Sekhar Ghosh, Anubha Gupta, Shweta Singh, 2023. A review on current epidemiology and molecular studies of lumpy skin disease virus-an emerging worldwide threat to domestic animals. Journal of medical pharmaceutical and allied sciences, V 12 - I 1, Pages - 5635 – 5643.DOI: 10.55522/jmpas.V12I1.4583.

57. Pate S, Dubey A, Gupta Ak, Ghosh NS, (2023). Evaluation of Antimicrobial Activity of Calotropis Gigantea Extracts on Two Main Skin Infection Causing Bacteria - Escherichia Coli and Staphylococcus Aureus.12(1):145-157.

58. Dubey A, Ghosh NS, Singh R. Zebrafish as An Emerging Model: An Important Testing Platform for Biomedical Science. J Pharm Negative Results 2022;13(3): 1-7.DOI:10.47750/pnr.2022.13.03.001.

59. Anubhav Dubey, Raghuvendra Singh, Ashish Kumar, Gaurav Mishra, Anubha Gupta, Anuj Sonker, & Amit Mishra. (2022). A Critical Review on Changing Epidemiology of Human Monkeypox-A Current Threat with Multi-Country Outbreak. *Journal of Pharmaceutical Negative Results*, 660–671. Retrieved from https://www.pnrjournal.com/index.php/home/article/view/738.

60. Dubey, A., Yadav, P., Peeyush, , Verma, P., & Kumar, R. (2022). Investigation of Proapoptotic Potential of Ipomoea carnea Leaf Extract on Breast Cancer Cell Line. *Journal of Drug Delivery and Therapeutics*, *12*(1), 51-55. https://doi.org/10.22270/jddt.v12i1.5172

61. Arun Kumar, Arpit Katiyar, Vijay Gautam, Rashmi Singh, & Anubhav Dubey. (2022). A Comprehensive Review on Anti-Cancer Properties of Amaranthus viridis. Journal for Research in Applied Sciences and Biotechnology, 1(3), 178–185. https://doi.org/10.55544/jrasb.1.3.23

62. Dubey Anubhav Ghosh Sekhar Niladry, Saxena Gyanendra Kumar, Purohit Debashis, Singh Shweta, (2022) .Management implications for neurotoxic effects associated with antibiotic use. NeuroQuantology, 6(20), 304-328. doi: 10.14704/nq.2022.20.6.NQ22034.

63. Dubey, A., Ghosh, N. S., Rathor, V. P. S., Patel, S., Patel, B., &Purohit, D. (2022).Sars- COV-2 infection leads to neurodegenerative or neuropsychiatric diseases. International Journal of Health Sciences, 6(S3), 2184–2197. https://doi.org/10.53730/ijhs.v6nS3.5980.

64. Kumar, A.., Dubey, A.., & Singh, R. . (2022). Investigation on Anti-Ulcer Activity of Momordica dioica Fruits in Wistar Rat. International Journal for Research in Applied Sciences and Biotechnology, 9(1), 105–111. https://doi.org/10.31033/ijrasb.9.1.12

65. Dubey Anubhav, Tiwari Mamta, Kumar Vikas, Srivastava, Kshama, Singh, Akanksha. Investigation of Anti-Hyperlipidemic Activity of Vinpocetine in Wistar Rat.International Journal of Pharmaceutical Research 2020; 12(02):1879-1882. DOI:https://doi.org/10.31838/ijpr/2020.12.02.250.

66. Raj, A., Tyagi, S., Kumar, R., Dubey, A., &Hourasia, A. C. (2021). Effect of isoproterenol and thyroxine in herbal drug used as cardiac hypertrophy. *Journal of Cardiovascular Disease Research*, 204-217.

67. Neeraj kumar, Anubhav Dubey, Ashish Mishra, Pallavi Tiwari. Formulation and Evaluation of Metoprolol Succinate Loaded Ethosomal Gel for Transdermal Delivery. JCR. 2020; 7(6): 1772-1782

68. Singh Shweta , Dwivedi Dr jyotsana, Tripathi Devika, Verma Priyanka, Ghosh Sekhar Niladry, Dubey Anubhav(2022). Nanorobotos is an Emerging Technology applicable in the Diagnosis and Treatment of Neuronal and Various Disease, NeuroQuantology, 6(20), 1081-1096.doi: 10.14704/nq.2022.20.6.NQ22100.

69. KHUSHNUMA RASHEED, DAKSHINA GUPTA, DR. ABHINAV PRASOON MISHRA, ANUBHAV DUBEY. (2021). Evaluation of hypoglycemic potential of β Escin. Annals of the Romanian Society for Cell Biology, 25(6), 13965–13975. Retrieved from https://www.annalsofrscb.ro/index.php/journal/article/view/8259.

70. Gaurava Srivastav, Dakshina Gupta, Anubhav Dubey, & Neeraj Kumar. (2022). Investigation of Anti- Pyretic Activity of Cinnamon Oil in Wistar Rat. Journal for Research in Applied Sciences and Biotechnology, 1(3), 51–56. https://doi.org/10.55544/jrasb.1.3.7

71. Kumar, N., Dubey, A., Mishra, A., & Tiwari, P. (2020). Ethosomes: A Novel Approach in Transdermal Drug Delivery System. *International Journal of Pharmacy & Life Sciences*, *11*(5).

72. Dubey A., Kumar R., Kumar S., Kumar N., Mishra A., Singh Y. and Tiwari M. (2020). Review on Vinpocetine, Int. J. of Pharm. & Life Sci.,

11(5): 6590-6597.

73. Meher, C. P., Purohit, D., Kumar, A., Singh, R., & Dubey, A. (2022). An updated review on morpholine derivatives with their pharmacological actions. *International Journal of Health Sciences*, *6*(S3), 2218–2249. https://doi.org/10.53730/ijhs.v6nS3.5983.

74. Patnaik, S., Purohit, D., Biswasroy, P., Diab, W. M., & Dubey, A. (2022). Recent advances for commedonal acne treatment by employing lipid nanocarriers topically. International Journal of Health Sciences, 6(S8), 180–205. https://doi.org/10.53730/ijhs.v6nS8.9671

75. Anubhav Dubey, Deepanshi Tiwari, Kshama Srivastava, Om Prakash and Rohit Kushwaha. A discussion on *vinca* plant. J PharmacognPhytochem 2020;9(5):27-31.

76. Dubey Anubhav , Kumar Abhay , Peeyush, Singh Jitendra, Medicinal property of Callistemon viminalis, International Journal of Pharmacognosy and Life Science 2021; 2(2): 15-20. DOI: https://doi.org/10.33545/27072827.2021.v2.i2a.35.

77. Yadav Priyanka, Dubey Anubhav, Formulation and characterization of anti-epileptic drug transdermal patch for enhance skin permeation, European Journal of Biomedical and Pharmaceutical Sciences 2021: 8, (9), 784-790. http://www.ejbps.com.

78. Prerna, Dubey Anubhav , Gupta Ratan, Nanoparticles: An Overview, Drugs and Cell Therapies in Haematology2021;10(1),1487-1497.

79. Dubey, Anubhav, Niladry Sekhar Ghosh, Nidhee Agnihotri and Amit Kumar et al. "Herbs Derived Bioactive Compounds and their Potential for the Treatment of Neurological Disorders." Clin SchizophrRelat Psychoses 16 (2022). Doi: 10.3371/CSRP.DANG.081922.

80. Kumari, M., Dubey, A., Agarwal, S., Kushwaha, S., & Sachan, A. K. (2023). Recent Technology and Software for GDP in the Pharmaceutical Industry. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN), 16(5), 7004–7007. https://doi.org/10.37285/ijpsn.2023.16.5.9

81. Dubey, A., Ghosh, N. S.., & Singh, R.S., (2023).Effects of aqueous and ethanolic seed extract of Asparagus racemosus Linn on neurobehavioral pattern of acrylamide induced experimental Zebra fish. Research Journal of Biotechnology.18(11),81-88. https://doi.org/10.25303/1811rjbt081088.

82. Dubey, A., Ghosh, N. S.., & Singh, R.S., (2023).Role of Aqueous and Ethanolic Seed Extract of Asparagus racemosus on Acr- Induced Neurotoxicity in Adult Zebrafish: Emergence of Neuroprotective Results. Egyptian Journal of Aquatic Biology & Fisheries,27(6), 285-296.DOI: 10.21608/EJABF.2023.329192

83. Dwivedi S., Bais N., Chhabra G., Joshi D., Jadhav5 S.A., Dubey A., Chhajed M. (2024). Investigation of Antiulcer Activity of Leonotisnepetaefolia (L.) R.Br. in Pylorus ligation induced and Ethanol induced Gastric ulcer in rats. Afr.J.Bio.Sc. 6(4):446-451. doi.org/10.33472/AFJBS.6.4.2024.231-240

84. Kumari M., Mishra G., Shukla D., Dwivedi M., Ghosh N., Tripathi A.K., HDubey A. (2024). A Novel scientific Approach: Zebrafish as an Informative in-vivo testing platform in Physiological Investigation. Afr.J.Bio.Sc. 6(4) (2024) 231-240. doi.org/10.33472/AFJBS.6.4.2024.231-

85. Gautam, M. K., Panda, P. K., Dubey, A., Kumari, M., & Ghosh, N. S. (2024). Zebrafish as a Fascinating Animal Model: A Robust Platform for in vivo Screening for Biomedical Research. International Journal of Pharmaceutical Investigation, 14(3), 696–701. https://doi.org/10.5530/ijpi.14.3.80

86. Deshmukh, R., Verma, S., Yaduwanshi, P. S., Dubey, A., & Kumari, M. (2025). Molecular-targeted Therapy for Precision Medicine in Gastrointestinal Cancer: Advancement in Cancer Targeting Strategies. *Current cancer drug targets*, 10.2174/0115680096333058241114064802. Advance online publication. https://doi.org/10.2174/0115680096333058241114064802

87. Gupta, J. K., Singh, K., Bhatt, A., Porwal, P., Rani, R., Dubey, A., Jain, D., & Rai, S. N. (2024). Recent advances in the synthesis of antidepressant derivatives: pharmacologic insights for mood disorders. *3 Biotech*, *14*(11), 260. https://doi.org/10.1007/s13205-024-04104-5

88. Singh, K., Gupta, J. K., Shrivastava, A., Jain, D., Yadav, A. P., Dwivedi, S., Dubey, A., & Kumar, S. (2025). Exploring the Pharmacological Effects of Bioactive Peptides on Human Nervous Disorders: A Comprehensive Review. *CNS & neurological disorders drug targets*, *24*(1), 32–46. https://doi.org/10.2174/0118715273316382240807120241

89. Thalluri, C., Vasam, M., Jampala, R., Alagarsamy, S., Dubey, A., Lather, A., & Hooda, T. (2024). Formulation, Development, and Optimization of Fast Dissolving Tablets Containing Tapentadol Hydrochloride. *Pharmaceutical nanotechnology*, 10.2174/0122117385350217241122151638. Advance online publication. https://doi.org/10.2174/0122117385350217241122151638

90. Batt, A., Singh, K., Gupta, J. K., Chanchal, D. K., Kumar, K., Dubey, A., Jain, D. (2024). A comprehensive review of cellular stress response pathway system of Rhizomacoptidis. Pharmacological Research - Modern Chinese Medicine, 100491. https://doi.org/10.1016/j.prmcm.2024.100491

91. Kumar A, Chaudhary JS, Dubey A, Pachorkar SS. Nanotechnology in Ankylosing Spondylitis: Advancements in Drug Delivery and Targeted Therapy. International Journal of Drug Delivery Technology. 2024;14(2):1162-1173.

92. Kumar P, Savita KK, Dubey A, Gaur SS. Unlocking Dithranol's Potential: Advanced Drug Delivery Systems for Improved Pharmacokinetics. International Journal of Drug Delivery Technology. 2024;14(2):1174-1180.

93. Jitendra Singh Chaudhary, Rohit Verma, Dilip Kumar Chanchal, Miss Seema Sahu, Soumya Ranjan Mishra, Vivek Tomar, Mahima Pandey, Anubhav Dubey and Shahbaz Khan (2024) Development and optimization of extended-release tablets using biodegradable natural binders for enhanced antidiabetic therapy. Biochem. Cell. Arch. 24, 2575-2579. https:// doi.org/10.51470/bca.2024.24.2.2575

94. Niladry S. Ghosh, Priteesachan, Radha Pal, Anubhav Dubey, Mamta Kumari (2024). Rudraksha: A Smart Drug And A Smart Nutrients: A Review. Library Progress International, 44(2), 1030-1045.

95. Yamoah J, Nyarko RO, Boateng PO, Boateng EA, Dubey A. Infertility: An observational study from the work of Yamoah J (1989) to modern times. International Journal of Pharmaceutical Science and Medicine 2024; 2(2): 44-52.

96. Dubey A, Ghosh NS, Mishra A, Kumari M, Sahu VK. Preclinical evaluation of *Asparagus racemosus*seed oil extract's wound healing efficacy. International Journal of Pharmaceutical Science and Medicine 2024; 2(2): 40-43.

97. Niladry SG, Anubhav D and Mamta K. Preclinical Evaluation of Asparagus Racemosus Seed Oil Extract's In Vitro Anti Salmonella Efficacy. Biodiversity Online J. 5(1). BOJ. 000603. 2024. DOI: 10.31031/BOJ.2024.05.000603