The Role of Protein Binding in Drug Pharmacokinetics Implications for Drug Efficacy and Safety

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Abstract

Protein binding is a critical factor in drug pharmacokinetics, significantly impacting drug absorption, distribution, metabolism, and excretion. This phenomenon refers to the reversible interaction between drugs and plasma proteins, such as albumin and alpha-1 acid glycoprotein, influencing drug efficacy and safety. A drug's free (unbound) fraction is pharmacologically active, while the bound fraction acts as a reservoir, modulating the drug's duration of action. Factors such as drug properties, protein levels, drug interactions, and pathological conditions can alter protein binding, leading to therapeutic effects and toxicity changes. Clinically, changing the dose and keeping an eye on the therapeutic drug are essential ways to handle drugs that bind to proteins, especially ones with a narrow therapeutic index, like warfarin and phenytoin. Understanding protein binding dynamics is also critical in drug development, ensuring optimal dosing regimens and minimizing the risk of adverse outcomes. This article explores the mechanisms and factors affecting protein binding and the clinical implications for drug efficacy and safety.

Keywords: Protein binding, free drug fraction, drug efficacy, drug safety, therapeutic drug monitoring (TDM)

Introduction:

Absorption, distribution, metabolism, and excretion (ADME) are the four stages of drug metabolism that the body goes through to determine how quickly and effectively a drug reaches its target site, how long it remains active, and how it is eventually eliminated from the body. Pharmacokinetics is a branch of pharmacology that studies these stages of drug metabolism [1]. Pharmacokinetics is a crucial field of study since it directly affects a medicine's therapeutic efficacy and potential for adverse drug reactions [2]. Following a drug's absorption into the systemic circulation, protein binding occurs in the bloodstream and interacts with several plasma proteins, including albumin, lipoproteins, and alpha-1 acid glycoprotein [3]. This reversible interaction suggests that the medicine binds to these proteins and can readily come loose.

Protein binding determines a drug's bioavailability or the proportion of its active form in the blood. The drug's unbound, or free, form is necessary to cross cell membranes, enter target tissues, interact with receptors, and have the desired therapeutic effects. The bound form of the drug, on the other hand, is pharmacologically inactive and functions as a reservoir, releasing the drug gradually and helping to maintain constant drug concentrations over time [4]. The proportion of protein binding varies substantially amongst drugs. Certain drugs, like warfarin, are up to 99% bound to plasma proteins, meaning very little is in circulation in their free, active form. Some drugs, like acetaminophen, only bind to small amounts of proteins, which keeps most of the drug active [5]. Protein binding has effects that go beyond only how drugs are distributed. It also affects how the kidneys and liver handle and eliminate drugs. Because only the free drug may be eliminated or

metabolized, the rate at which these processes occur can be affected by variations in the degree of protein binding.

Additionally, changes in protein binding due to physiological or pathological factors may alter the safety and efficacy of medications, possibly leading to side effects or ineffectiveness [6]. Understanding the role of protein binding in drug pharmacokinetics is essential for improving drug therapy, especially when working with medications with a narrow therapeutic window, meaning that small changes in plasma concentration can significantly affect toxicity and therapeutic effects.

Mechanism of Protein Binding

A drug's effects on the body are inconsistent once it enters the systemic circulation. Instead, it is found in a precarious equilibrium between bound and unbound (free) states. The way that medications work and are distributed, digested, and removed all depend on this balance between the two states.

Bound vs. Unbound Drug: The Distinction

The pharmacologically active form of a medication is its unbound or free form. This form can get past biological barriers like cell membranes to the site of action, where it binds to particular cell receptors to carry out pharmacological or therapeutic actions. Additionally, only the unbound fraction is susceptible to enzyme breakdown, primarily in the liver, and elimination by the kidneys or bile. Therefore, the strength and durability of the medicine's therapeutic benefits are frequently strongly correlated with free drug concentrations.

On the other hand, because the bound medication is bound to plasma proteins such as albumin, alpha-1 acid glycoprotein, or lipoproteins, it is pharmacologically inert. Since the drug-protein complex is usually too big to interact with receptors or pass through cell membranes, the bound drug cannot produce pharmacological effects immediately. But it serves as a reservoir, gradually releasing little medication to top off the free portion during metabolism or excretion. For some medicines, this gradual release can help prolong the effect, maintaining consistent therapeutic levels for longer [7].

Plasma Proteins and Their Binding Preferences

Due to their distinct chemical characteristics, several blood plasma proteins show affinity for particular drug classes:

1. **Albumin:** Mostly binding to acidic medicines, albumin is the most prevalent plasma protein in human blood. Aspirin, phenytoin, and warfarin are a few examples. A significant portion of medications in circulation can be carried by albumin because of its many binding sites, particularly acidic and lipophilic.
2. **Alpha-1 acid glycoprotein** binds to essential medications, including imipramine, lidocaine, and propranolol, more selectively. Drug binding may be impacted by elevated alpha-1 acid glycoprotein levels in pathological states such as infection or inflammation.
3. **Lipoproteins and globulins:** Fat-soluble lipophilic medications can bind to blood lipoproteins. Medications like amphotericin B and cyclosporine show this type of interaction.

   How long a medication is active in the body, how much of it is available to exert therapeutic effects, and how the drug is eliminated from the body are all critically influenced by the degree of protein binding [8].

Dynamic Nature of Protein Binding

A medication and plasma proteins can interact reversibly. This reversibility maintains the dynamic equilibrium between a drug's bound and unbound fractions. The balance changes as free drug molecules are broken down or eliminated, releasing more medications from the bound state to keep the proper concentration of free drugs in the body. For medicines with extended half-lives, the capacity to continually replenish free drug

concentrations is especially crucial since it helps maintain therapeutic levels without requiring frequent dosing.

Highly protein-bound medications (like warfarin, which is up to 99% bound) have a limited amount of free circulation at any given moment, which slows down their clearance and may extend their effects. On the other hand, most drugs are unbound and ready for instant action and faster removal when it comes to medications with poor protein binding, such as acetaminophen [9].

Factors Influencing Protein Binding

1. **Drug Concentration and Affinity**: The amount of medication that can bind to plasma proteins varies depending on its circulation level. In general, more excellent binding happens when drug concentrations increase. On the other hand, at high concentrations, protein binding sites might become saturated, increasing the fraction of free drugs. The affinity with which drugs attach to plasma proteins also varies. For example, acetaminophen has a significantly lower affinity for albumin than warfarin, suggesting that more of it can circulate in the free form. Warfarin has a relatively high affinity for albumin, meaning that most is bound.
2. **Drug Properties**

The intrinsic properties of a drug significantly affect its binding to plasma proteins. These properties include:

- **Lipophilicity**: Unlike hydrophilic (water-soluble) medicines, lipophilic (fat-soluble) medications typically bind to plasma proteins more extensively. It's due to the hydrophobic pockets of plasma proteins, such as albumin, which easily interact with lipophilic medications. Strong protein binding is seen by highly lipophilic drugs like warfarin and diazepam, which cause a delayed release into the bloodstream and prolonged activity. Hydrophilic medications, such as acetaminophen, on the other hand, have less protein binding and are easier to find in their free form.
- **Molecular Size**: Compared to smaller molecules, larger drug molecules have a higher affinity for plasma proteins. Bigger medications might engage with proteins at several locations, stabilizing the drug-protein combination. The quantity of free medication that is accessible for pharmacological action or excretion is decreased by this binding.
- **Ionization**: Drugs that display differential binding to plasma proteins are frequently ionized (charged) at physiological pH. Essential medications like propranolol tend to bind to alpha-1 acid glycoprotein, whereas acidic medications like phenytoin usually bind to albumin. Protein binding may thus be impacted by the degree of ionization, which depends upon the blood pH and the pKa of the medication. While weak bases are more likely to bind to alpha-1 acid glycoprotein, weak acids are more likely to bind to albumin.

3. **Plasma Protein Levels**

The amount of drug binding largely depends on the concentration of plasma proteins, especially alpha-1 acid glycoprotein, and albumin. Drug binding can be considerably altered by variations in plasma protein levels brought on by several conditions:

- **Low Albumin Levels (Hypoalbuminemia)**: The most prevalent plasma protein, albumin, binds many medications, especially acidic ones. Albumin levels may be lowered in liver disease, malnourishment, nephrotic syndrome, or burns. A higher free drug fraction results from this reduction in binding sites. These sites can both increase the risk of toxicity and improve the pharmacological impact of the medicine. For example, strongly bound medications such as phenytoin or warfarin may exhibit elevated free concentrations in hypoalbuminemia patients, which may result in side effects such as bleeding or neurological problems.
- **Elevated Alpha-1 Acid Glycoprotein Levels**: On the other hand, acute circumstances like trauma, infection, or inflammation may cause an increase in alpha-1 acid glycoprotein levels. Primarily, this protein binds simple medications like lidocaine and propranolol. The rise in drug binding caused by the

elevation in alpha-1 acid glycoprotein levels lowers the free fraction and may lessen the therapeutic impact of the medicine. Higher doses may be required to achieve the intended pharmacological effect [10].

4. Competition for Binding Sites

The same locations on plasma proteins, mainly albumin, are where many medications bind. When two or more medications are given together, they may compete for the same binding sites, which could cause one medication to replace the other. When a drug is displaced, its free concentration may rise. These could have severe therapeutic ramifications, particularly for medicines with a limited therapeutic index.

- **Narrow Therapeutic Index Drugs**: Digoxin, phenytoin, and warfarin are drugs with a narrow therapeutic index (NTI) that need to be closely monitored since even slight variations in their free concentration can significantly negatively impact toxicity or therapeutic failure. For instance, an NSAID like ibuprofen may cause warfarin to be displaced from its binding sites if a patient is taking warfarin, which is firmly bound to albumin along with it. Severe bleeding is more likely as a result of this displacement, which also raises the free warfarin concentration.
- **Drug-Drug Interactions**: In polypharmacy, or the use of many medications, displacement interactions are clinically relevant, particularly in older patients or those with chronic illnesses. To prevent negative consequences from a fast increase in free drug concentrations, it is crucial to understand possible drug-drug interactions [11].

5. Pathophysiological Conditions

Different illness conditions can modify plasma protein levels or drug-binding capacity, leading to significant changes in protein binding. These circumstances may exacerbate pharmacokinetics and result in unanticipated medication reactions.

- **Renal Failure**: Protein binding is altered in renal disease, especially chronic kidney disease. This is primarily because of variations in plasma protein levels and the buildup of endogenous compounds that may compete for binding sites. These modifications may raise the free fraction of some medications, like phenytoin and furosemide, increasing the risk of toxicity. Renal failure also inhibits the body's ability to eliminate drugs, which, when paired with changed protein binding, can lead to prolonged drug activity or buildup.
- **Hepatic Impairment**: The liver produces many plasma proteins, including albumin. They reduced albumin production in liver illnesses like cirrhosis or hepatitis, resulting in higher quantities of free drugs and decreased protein binding. The metabolism of drugs may also be impacted by hepatic dysfunction, which would further complicate medication pharmacokinetics. Patients with liver disease may need to change their dosages of medications like theophylline and diazepam, which are both heavily protein-bound and processed by the liver, to avoid toxicity.
- **Blood pH Changes**: Drugs' ionization states can be impacted by changes in blood pH, such as those caused by acidosis or alkalosis, which can change how well-suited they are for plasma proteins. For instance, essential medications may be displaced from alpha-1 acid glycoprotein during acidosis, increasing their free concentrations, whereas acidic pharmaceuticals are more likely to attach to albumin. This may have significant clinical ramifications, particularly for medications like morphine or lidocaine, where exact dosage is essential.

5. Saturation of Binding Sites

Protein binding is often non-saturable at low drug concentrations, meaning that a proportionate amount of the drug binds to the accessible protein as the concentration rises. However, the number of available binding sites may become saturated as medication concentrations rise. As more of the medication remains unbound due to this saturation, the free fraction of the drug increases nonlinearly. This phenomenon is significant for medications like valproic acid, which is strongly protein-bound or given in large dosages.

Importance of Protein Binding in Clinical Practice

Protein binding has critical clinical ramifications, especially for medications with narrow therapeutic indices (NTIs), in which even little variations in drug concentration might result in toxicity or therapeutic failure. This group of drugs includes warfarin, phenytoin, and digoxin; modifications to their binding dynamics may have a significant impact on the safety and effectiveness of these medications. Therapeutic drug monitoring (TDM) is frequently employed in clinical practice for medicines with a limited therapeutic window and high protein binding. Healthcare practitioners can ensure optimal therapeutic outcomes while limiting the risk of side effects by properly adjusting doses based on total and free medication concentration measurements [12].

Implications for Drug Efficacy

The amount of a drug that is available in its free form that is pharmacologically active is directly impacted by the degree of protein binding, which also affects the drug's efficacy. The free drug fraction interacts with target receptors, penetrates biological membranes, and finally produces therapeutic effects. As a result, modifications in protein binding may significantly impact the medication's overall efficacy.

- **Prolonged Duration of Action**: Largely protein-bound medications, like diazepam (which binds to albumin very strongly), frequently have longer half-lives. The drug's bound component serves as a reservoir, gradually releasing the free drug into the bloodstream. This may lessen the need for frequent dosage and produce a more prolonged therapeutic impact. The slow release of diazepam from protein binding sites is primarily responsible for its extended half-life.
- **Reduced Protein Binding and Enhanced Effects**: Protein availability for binding is reduced in some physiological or pathological circumstances, such as hypoalbuminemia (low albumin levels). Consequently, a higher percentage of the medication stays in its unbound state. For instance, individuals who suffer from malnourishment or liver disease frequently have lower albumin levels, which raises the free drug concentrations of highly protein-bound drugs like phenytoin. This could improve the therapeutic benefit, but if it's not closely watched, it can also raise the chance of toxicity and adverse effects. For some medications, even slight increases in free concentration can significantly impact safety and effectiveness.
- **Therapeutic Drug Monitoring (TDM)**: Medicinal professionals frequently utilize therapeutic drug monitoring to measure total and free drug concentrations for medications where protein binding is essential to the drug's effectiveness. This guarantees that the free fraction stays within the therapeutic range, which is necessary for patients interacting with several drugs or changing protein levels. Monitoring is particularly crucial for medications with a narrow therapeutic index, where even small changes in free concentration might have hazardous or subtherapeutic consequences [13].

Implications for Drug Safety

Additionally, protein binding is critical in preserving drug safety, particularly for drugs with narrow therapeutic indices (NTIs), which denote a relatively narrow range between a drug’s therapeutic and hazardous levels. Changes in the binding of proteins can give rise to serious safety concerns:

- **Risk of Toxicity**: Highly protein-bound medications, like warfarin (97–99% bound to albumin), can become hazardous if they are removed from their binding sites, which causes the concentration of the free drug to spike. For instance, warfarin is frequently used as an anticoagulant. Still, if its protein binding is interfered with by competing medications or changes in albumin levels, the resultant rise in free warfarin can cause severe bleeding. For this reason, even slight modifications in protein binding for NTI medications must be carefully controlled.
- **Drug-Drug Interactions**: Drug-drug interactions are also significantly influenced by protein binding. When combined, drugs can compete for binding sites if they bind to the same plasma protein. One medication may be displaced as a result of this competition, increasing the drug’s free concentration and

perhaps increasing its toxicity. For instance, ibuprofen and other nonsteroidal anti-inflammatory medicines (NSAIDs) can replace albumin with warfarin, increasing the risk of hemorrhagic consequences. When medications like phenytoin or sulfonamides are taken with other highly protein-bound drugs, similar interactions may happen.

- **Special Populations and Vulnerable Patients**: Protein-binding alterations can be especially dangerous for specific patient populations, such as those with hepatic or renal impairment. For example, the buildup of uremic toxins in renal failure might change how proteins bind to each other, increasing the amount of free medication and raising the risk of toxicity. Likewise, decreased albumin synthesis in people with hepatic impairment may impact the safety and binding of drugs such as valproic acid and diazepam. To prevent negative consequences, these conditions necessitate dose modifications and careful observation.
- **Monitoring and Prevention of Adverse Effects**: Clinicians need to be aware of a patient's general state, including protein levels, renal and hepatic function, and potential drug interactions, to reduce the risk of toxicity resulting from changes in protein binding. Therapeutic drug monitoring (TDM) can be used to guarantee safe drug concentrations when drug displacement or changed protein binding is probable. To avoid side effects, prescription dosage adjustments or switching to fewer protein-binding drugs may be required, as shown in Figure 1 [14].

Figure 1: Altered Pharmacokinetics in geriatrics

1. Older adults (>65) may experience more adverse reactions and drug-drug interactions due to several factors listed here.
2. In older adults, decreased gastric function affects the rate of drug absorption, altered body fat, decreased total body water, reduced serum albumin affects drug distribution, decreased hepatic metabolism can prolong drug responses and increase half-life, and decreased renal function affects rates of drug excretion.
3. Polypharmacy is the simultaneous use of multiple drugs for a single condition.
4. Adherence, not taking all medications consistently
5. Low Therapeutic Index: use of drugs with a low/narrow therapeutic index
6. Severe Illness, concomitant severe illnesses

Clinical Considerations and Adjustments

Drug pharmacokinetics are greatly influenced by protein binding, and changes in this binding may require particular clinical modifications to provide the best possible patient outcomes. Drugs that significantly bind

to proteins and those used in populations with altered physiological conditions, including liver or renal Illness, require specific attention. Important clinical guidelines for administering medications impacted by protein binding:

1. Modifications to Dosage:

Dosage adjustments may be necessary for patients whose conditions, physiological changes, or drug interactions affect protein binding to preserve therapeutic efficacy and avoid toxicity. This is especially crucial for medications with limited therapeutic windows, as even minute variations in the free drug concentration might have adverse effects. Dosage modifications are necessary for several ailments and situations, including:

- **Hepatic Disease:** Reduced albumin production in patients with hepatitis or liver cirrhosis can result in less protein binding, raising the free drug concentration. It may be necessary to lower the dosage of medications that are highly protein-bound, including valproic acid and phenytoin, to avoid toxicity.
- **Renal Failure:** The buildup of metabolic waste products in kidney failure patients can change how proteins bind to one another. The pharmacokinetics are further complicated by decreased renal clearance. In such patients, dosage reductions or closer monitoring may be necessary for medications like digoxin or furosemide to avoid buildup and toxicity.
- **Drug Interactions:** Competitive displacement can happen when many medications that bind to the same protein are taken simultaneously. For instance, NSAIDs and warfarin both bind to albumin and taking these medications at the same time may raise the risk of bleeding by increasing the amount of free warfarin in the body. Lower dosages or more caution is required in these situations.

  Monitoring free drug levels in clinical practice can give more precise instructions for changing dosages. Free medication concentration is beneficial when displacement interactions are probable or in patients with hypoalbuminemia [15].

2. Therapeutic Drug Monitoring (TDM)

Therapeutic Drug Monitoring (TDM) is essential for medications with limited therapeutic indices and high protein binding. Rather than only measuring the overall drug concentration in the blood, TDM measures the free (unbound) drug levels as well. With this method, the pharmacologically active portion of the medication is more accurately reflected, allowing for more precise dose modifications that maximize effectiveness and reduce toxicity risk.

- **Phenytoin:** Because it is an anticonvulsant with a high protein binding affinity, albumin levels and medication interactions can significantly affect the free drug concentration of phenytoin. TDM is essential for keeping levels at the right place to stop seizures without having adverse side effects, including depression of the central nervous system.
- **Warfarin:** Because of its broad protein binding and narrow therapeutic index, warfarin is a top contender for treating type 2 diabetes. Decreased free warfarin levels even slightly increase the risk of thrombosis or bleeding. Clinicians can modify dosages by routinely checking free medication levels and the INR (International Normalized Ratio).
- **Valproic Acid:** In a similar vein, those with altered protein binding, such as the elderly or those suffering from liver disease, must take valproic acid, an anti-epileptic medication, with TDM. By monitoring free drug levels, it is possible to keep the drug from building up to dangerous levels in these susceptible groups. Clinicians can optimize treatment plans using TDM, especially in complicated situations like multi-drug therapy or patients with underlying illnesses that impact protein binding [16].

3. Drug Development

Determining a drug's pharmacokinetic profile, dose, and potential for drug interactions throughout the drug development process requires an understanding of the protein-binding properties of the drug. High protein binding drugs may provide significant difficulties, especially in maintaining sufficient therapeutic efficacy while lowering the risk of harm. A few things to think about are:

- **Formulation:** It could be necessary to consider the gradual release of medications from plasma proteins when formulating drugs with high protein binding. This may impact the creation of formulations with controlled or extended-release.
- **Dosage Regimens:** Particular attention needs to be paid to dosage schedules for strongly protein-bound medications. Because of the delayed release of the bound fraction, these medications frequently have longer half-lives, requiring less frequent dosage. On the other hand, developers need to consider higher free drug concentrations when there is reduced protein binding, such as hypoalbuminemia, as this may require lower or more customized doses.
- **Drug Interactions:** Assessing any possible drug-drug interactions that can impact protein binding throughout preclinical and clinical trials is critical. The pharmacokinetics of the experimental medicine may be affected by the co-administration of other pharmaceuticals that bind to the same protein, requiring dose modifications or contraindications with other medications.
- **Special Populations:** When developing new drugs, particular populations like the elderly, pregnant women, and patients with liver or kidney illness must be taken into account. It is possible to create safe and efficient dosage schedules for every patient group by thoroughly understanding how protein binding varies in different populations [17].

Conclusion

Protein binding is a critical determinant of drug pharmacokinetics, significantly impacting both efficacy and safety. The interplay between bound and free drug fractions governs how a drug is distributed, metabolized, and excreted, with the free fraction being pharmacologically active. Changes in protein binding due to disease states, drug interactions, or altered physiological conditions can lead to variations in the free drug concentration, affecting therapeutic outcomes. Drugs with high protein binding may have prolonged effects due to the reservoir of bound medications. Still, reduced binding can increase the risk of toxicity, especially in drugs with a narrow therapeutic index like warfarin and phenytoin.

For clinicians, managing protein binding is essential to optimize drug therapy. Dose adjustments and therapeutic drug monitoring (TDM) are crucial strategies, particularly in patients with liver or kidney disease or multiple medications. Understanding protein binding is essential in drug development for designing effective dosing regimens and anticipating drug interactions. Ultimately, by recognizing and managing the complexities of protein binding, healthcare providers can improve therapeutic efficacy, minimize adverse effects, and enhance patient safety across various clinical settings.

References:

1. J. E. Riviere, "Absorption, distribution, metabolism, and elimination," *Veterinary Pharmacology and Therapeutics*, 9th ed., 2009.
2. K. Tsaioun, B. J. Blaauboer, and T. Hartung, "Evidence-based absorption, distribution, metabolism, excretion (ADME) and its interplay with alternative toxicity methods," *ALTEX-Alternatives to Animal Experimentation*, vol. 33, no. 4, pp. 343-358, Nov. 2016.
3. A. K. Skulberg, I. Tylleskar, T. Nilsen, S. Skarra, Ø. Salvesen, T. Sand, T. Loftsson, and O. Dale, "Pharmacokinetics and dynamics of intramuscular and intranasal naloxone: an explorative study in healthy volunteers," *Eur. J. Clin. Pharmacol.*, vol. 74, pp. 873–883, Jul. 2018.
4. M. A. Alam, F. I. Al-Jenoobi, A. M. Al-Mohizea, and R. Ali, "Understanding and managing oral bioavailability: physiological concepts and patents," *Recent Patents on Anti-Cancer Drug Discovery*, vol. 10, no. 1, pp. 87-96, Jan. 2015.
5. G. Lambrinidis, T. Vallianatou, and A. Tsantili-Kakoulidou, "In vitro, in silico and integrated strategies for the estimation of plasma protein binding. A review," *Advanced Drug Delivery Reviews*, vol. 86, pp.

27-45, Jun. 2015.

6. A. N. Deitchman, R. S. Singh, and H. Derendorf, "Nonlinear protein binding: not what you think," *Journal of Pharmaceutical Sciences*, vol. 107, no. 7, pp. 1754-1760, Jul. 2018.
7. H. D. Lagassé, A. Alexaki, V. L. Simhadri, N. H. Katagiri, W. Jankowski, Z. E. Sauna, and C. Kimchi-Sarfaty, "Recent advances in (therapeutic protein) drug development," *F1000Research*, vol. 6, 2017.
8. C. Gay, D. Toulet, and P. Le Corre, "Pharmacokinetic drug-drug interactions of tyrosine kinase inhibitors: A focus on cytochrome P450, transporters, and acid suppression therapy," *Hematological Oncology*, vol. 35, no. 3, pp. 259-280, Sep. 2017.
9. S. Ambadipudi and M. Zweckstetter, "Targeting intrinsically disordered proteins in rational drug discovery," *Expert Opinion on Drug Discovery*, vol. 11, no. 1, pp. 65-77, Jan. 2016.
10. H. Wen, H. Jung, and X. Li, "Drug delivery approaches in addressing clinical pharmacology-related issues: opportunities and challenges," *The AAPS Journal*, vol. 17, pp. 1327-1340, Nov. 2015.
11. S. Kosanam, "Drug interactions: A review with protein displacement drug-drug interaction," *Asian J. Pharm. Pharmacol.*, vol. 4, no. 3, pp. 252–255, 2018.
12. A. H. Lavan, J. O'Grady, and P. F. Gallagher, "Appropriate prescribing in the elderly: Current perspectives," *World Journal of Pharmacology*, vol. 4, no. 2, pp. 193-209, Jun. 2015.
13. K. Pathak and S. Raghuvanshi, "Oral bioavailability: issues and solutions via nanoformulations," *Clinical Pharmacokinetics*, vol. 54, pp. 325-357, Apr. 2015.
14. J. Posner, "Clinical pharmacology–the basics," *Surgery (Oxford)*, vol. 33, no. 3, pp. 104-111, Mar. 2015.
15. A. di Masi, V. Trezza, L. Leboffe, and P. Ascenzi, "Human plasma lipocalins and serum albumin: Plasma alternative carriers?" *Journal of Controlled Release*, vol. 228, pp. 191-205, Apr. 2016.
16. G. Baktır, "Therapeutic drug monitoring (TDM)," *Lectio Scientific*, vol. 1, no. 1, pp. 54-65, 2017.
17. L. Regan, D. Caballero, M. R. Hinrichsen, A. Virrueta, and C. S. O'hern, "Protein design: Past, present, and future," *Peptide Science*, vol. 104, no. 4, pp. 334-350, Jul. 2015.