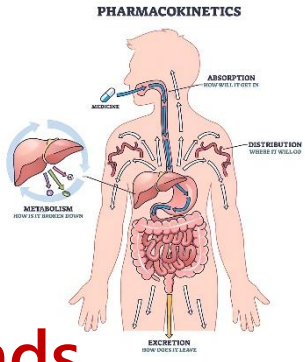

CHAPTER 03

Pharmacokinetics and Bioavailability of Natural Compounds

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ABSTRACT: Plant-based medicines have received significant attention in terms of therapeutic capabilities, however poor pharmacokinetics and low bioavailability of such compounds have often made it challenging to get benefit from their potential in the clinical setting. In this chapter, the basic pharmacokinetic processes, including absorption, distribution, metabolism, and excretion (ADME) of natural products are discussed. This chapter emphasizes how physicochemical properties, enzyme degradation, transport protein or inter-individual differences influence the systemic exposure of natural compounds to the body. Relative to synthetic drugs, natural compounds encounter several specialized challenges including, insolubility, poor stability, and extensive first-pass metabolism. To address these constraints, this chapter discusses a wide variety of bioavailability enhancement methods, including, nanocarriers, liposomes, self-emulsifying drug delivery systems (SEDDS), prodrug development, and enzyme inhibitors. Furthermore, latest trends in this field, such as AI-based pharmacokinetic modeling, personalized drug delivery, and precision medicine integration are also addressed in this chapter. Altogether, this chapter offers an overall picture of how optimization of pharmacokinetics will allow tapping the true potential of natural compounds in contemporary medicine.

Keywords: Bioavailability, Pharmacokinetics, Natural compounds, Drug development, Drug delivery

The use of plants in the treatment of different diseases is not a new concept. Historically, there is a wide range of scientific evidence that prove the pharmacological characteristics of the plants along with the therapeutic efficiency of natural products (Yuan et al., 2016; Ernst et al., 2015; Ahmed et al., 2025). According to the World Health Organization (WHO), it is estimated that 80 percent of the global population use plants today, mostly in the form of extract or active compounds for their use in curing prevalent illnesses (WHO 2018). Nevertheless, poor bioavailability (BA) and unpredictability of natural substances in the body remains a major problem faced during the development of drugs. Drug development activities are primarily concerned with the assessment of toxicity and effectiveness of new medication. In this regard, proper knowledge of pharmacokinetics (PK) and BA is essential. PK explains how body alters drug concentration, encompassing its absorption, distribution, metabolism and excretion. Conversely, BA is the amount of a drug that reaches circulation, and, is available at the site of action to exert its therapeutic actions (Lin & Lu, 1997).

Both, PK and BA are important factors in determining the safety and effectiveness of drugs during development phase. Understanding of PK principles results in quicker drug development, more economical drug use, and fewer side effects. Similarly, BA has a direct impact on the overall therapeutic result, safety, and efficacy of a medicine. Insufficient BA can impair therapeutic efficacy, while high drug concentration can lead to toxicity and adverse effects. Therefore, BA of the

How to Cite: Tabassum R, S Habib, A Ramzan, Z Godya, A Bibi, M Shaharyar, MZ Salar & A Wahab, 2025. Pharmacokinetics and Bioavailability of Natural Compounds. In: Natural Products in Biomedical Research (Ijaz MU & A Ashraf, Eds.): FahumSci, Lahore, Pakistan, pp: 27-38. ISBN: 978-627-7745-15-8. https://doi.org/10.61748/NPBR.2025/03

drugs must be considered while determining an effective therapy and dosage. However, a number of unique challenges emerge when these PK concerns are applied to natural compounds, which must be resolved to optimize their therapeutic capabilities (Bhandare & Nannor, 2024).

One prevalent obstacle, while evaluating the PK characteristics of natural medicines, is that the pharmacologically active ingredients are often unknown. Furthermore, the complexity of natural substances and the growing number of possible active ingredients make it difficult to determine the pharmacological foundation of their therapeutic properties. This poses another issue because it is difficult to accurately assess the amounts of the product's constituents in the absence of precisely defined target substances (Derendorf, 2012). Additionally, the absence of standardized processes, insufficient understanding of biological mechanisms, and the infrequent inclusion of controlled and documented clinical studies in accordance with standards, represent further challenges to the use of natural products as therapeutic agents (Ernst et al., 2015).

The chapter is intended to present these complications by providing case studies of natural compounds along with the recognition of the pharmacokinetic principles, variables that influence the BA of a natural compound, and the methods that could be employed to enhance BA. In addition, new developments in technology, tailored PK, in silico modeling, and other areas are explored to provide a new perspective. The ultimate goal of this chapter is to provide the readers with a comprehensive understanding of both the latest advancements aimed at enhancing the medicinal potential of natural compounds and their pharmacokinetic behavior.

OVERVIEW OF PHARMACOKINETIC PRINCIPLES

As we previously mentioned, PK is the fundamental field of pharmacology, that explains how the body responds to medications. The most crucial PK parameters that affect how medications behave in the body are ADME (absorption, distribution, metabolism, and excretion). To help drug research and development procedures for the creation of safer and more effective biotherapeutics, ADME characteristics must be thoroughly characterized and thoroughly studied. Additionally, ADME investigations have always been essential for improving the PK characteristics of novel medications and raising their success rate (Paul Gleeson et al., 2011). However, a thorough examination of each element is necessary to comprehend the significance of PK concepts in drug development.

Absorption

The process via which a drug enters the body's systemic circulation is called absorption. Although drugs may be absorbed through the skin, respiratory system, or gastrointestinal tract, they must pass through cell membranes, either passively or actively, to enter the systemic circulation. Nonetheless, a number of variables, including, route of administration, molecule size, gradient of concentration, degree of protein binding and lipid solubility, as well as first pass metabolism, affect the rate of absorption, thereby reducing the drug' BA (Bertram-Ralph & Amare, 2023).

Distribution

Once the drug has been absorbed, it transports through the bloodstream throughout the body. Numerous factors, including tissue permeability, blood flow, plasma protein binding, and physiological barriers, influence drug distribution. However, binding of plasma proteins between albumin and alpha-1-acid glycoprotein is the main distribution factor that controls drug distribution. Drugs with a high affinity for plasma proteins are less readily available, resulting in fewer pharmacological effects; in contrast, drugs that are weakly bound, enter more tissue spaces. Moreover, several factors including, drug ionization state, drug lipophilicity, and molecular size affect tissue penetration of the drugs. According to clinical research, hydrophilic drugs exhibit restricted penetration into bodily tissues and primarily remain in blood plasma and interstitial fluids, while lipophilic medications have high membrane permeability and thus a higher distribution rate (Stepensky, 2013).

Metabolism

The irreversible conversion of a drug into a metabolite that is easier to eliminate from the body,

primarily due to enzymatic processes, is known as metabolism. Drug metabolism usually occurs in two stages. The first stage is called Phase I biotransformation, in which the chemical introduces or reveals a functional group (-OH, -NH2, -SH) that is necessary for conjugation with an endogenous conjugating agent (Li et al., 2019). After undergoing phase I biotransformation, the drug passes through phase II biotransformation, in which a polar molecule, such as glutathione, sulfate, or glucuronic acid, is bonded to the drug or its Phase I metabolite. As a result, the molecule becomes more soluble in water and is easier to eliminate from the body, mostly through bile or urine (Pang & Durk, 2010).

Excretion

Excretion, or elimination, is the process by which drugs or their metabolites leave the body. The kidney and liver are the primary organs through which excretion occurs.

Renal excretion: Glomerular filtration is primarily used to remove substances that are charged or polar and do not bind well to plasma proteins. On the other hand, substances that are heavily attached to plasma proteins typically do not go through substantial filtration and instead stay in the blood. The cells of tubular wall extract certain medications from plasma and release them into the proximal tubules. Lipid-soluble compounds are inadequately removed by the kidneys, as they are extensively reabsorbed inside the tubules. The reabsorption of weak electrolytes is strongly influenced by pH. Weak acids are more ionized and thus are expelled more frequently if the tubular urine is made more alkaline. On the other hand, weak acids are less ionized and undergo reabsorption. Renal excretion is decreased if the tubular urine is made more acidic (Masereeuw & Russel, 2001).

Biliary excretion: The larger, protein bound, and lipophilic compounds are excreted into the bile (Meijer, 2010). After absorption, compounds pass from extensive hepatic metabolism before entering the bloodstream. The body then transports the metabolized drug from the bile to the intestine for elimination through feces. This route is typically used by polar and large-sized drugs Medications that are reabsorbed into the bloodstream from the intestines, however, have longer half-lives and more pronounced effects (Benedetti et al., 2009). Behavior of drugs has been illustrated in Fig. 1.

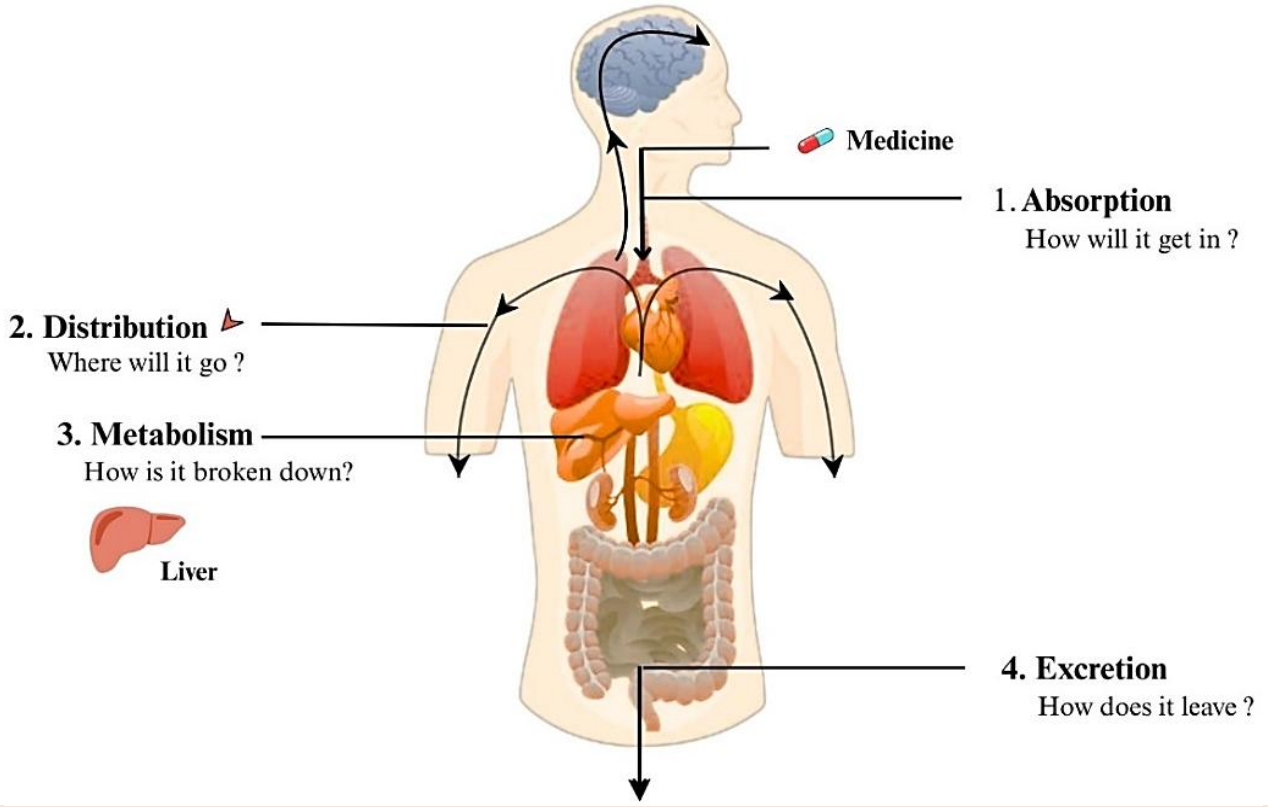

Fig 1. Pharmacokinetic behavior of drugs

FACTORS INFLUENCING BA OF NATURAL COMPOUNDS

Various factors including physiochemical properties, biological as well as physiological barriers have a substantial impact on the BA of natural compounds, which need to be carefully taken into account to ensure the best possible therapeutic effects.

Physicochemical Properties

Solubility: Solubility is a crucial physicochemical characteristic that influences substance absorption and BA. Substances must first dissolve sufficiently in the aqueous environment of GI lumen in order to be absorbed through the GI tract. Inadequate water solubility frequently leads to partial absorption and decreased BA. The BA of many natural compounds is severely limited by their low permeability across biological membranes and limited solubility in water (Azman et al., 2022).

Lipophilicity: The capacity of a molecule to dissolve in fats, oils, and non-polar solvents is known as lipophilicity. Lipophilic substances have low accessibility and poor solubility in GIT fluids, whereas, hydrophilic biomolecules are highly soluble but have difficulty in their penetration across the lipophilic epithelial cell bilayer. Thus, some bioactive substances (vitamin C and epigallocatechin-3-gallate [EGCG]) are highly soluble but have poor cell membrane permeability, while others (like curcumin) are poorly soluble and have low cell membrane permeability, and some, such as resveratrol, are poorly soluble but possess significant cell membrane permeability (Rezaei et al., 2019).

Molecular size and weight: Another significant factor that affects a molecule's capacity to diffuse passively through cell membranes is its size (Chillistone & Hardman, 2017). The rate of passive transport tends to reduce with increasing molecule size, which could affect oral BA (Yang & Hinner, 2014). Both the polar surface area or hydrogen bond count and the number of rotatable bonds typically increase with molecular weight. So, the substances having high molecular weight are less soluble in aqueous environment thereby, reducing BA (Veber et al., 2002).

Metabolic stability: One of the most important factors influencing BA is metabolic stability, which is the resistance of medicine to biotransformation by metabolic enzymes. This is especially important for oral medications that undergo first-pass metabolism in the liver and intestines before entering the bloodstream (Masimirembwa et al., 2003). Natural compounds have low metabolic stability; thus, their BA is reduced by this mechanism (Azman et al., 2022).

pH of the surrounding environment: The second element that favorably affects a molecule's solubility is its vulnerability to ionic dissociation. Compounds that exist as cations and anions typically tend to have higher solubility. Since the majority of organic substances are weak bases and acids. Consequently, the pH of the aqueous solution has a significant impact on their dissolution (Hamed et al., 2016).

Gut microbiota: The optimization of molecule delivery is significantly impacted by the gut microbiota, which is a crucial factor in the BA of drug. Bacterial metabolites can alter the local intestinal pH, which may impact drug solubility and absorption patterns. Additionally, medicines and bacterial products may compete for host metabolic enzymes, adding another level of complexity to the regulation of product BA (Wang et al., 2024).

Biological and Physiological Barriers

Gastro-intestinal environment: The GIT factors affecting the BA of the natural compounds are the physio-chemical and physiological conditions (mechanical forces, pH, chemical composition of the GIT fluids, presence of enzymes, surfactants, etc.) to which the food taken in is subjected to during its transport through the GIT. These factors have the potential to influence several characteristics of a compound, such as its solubility, release, chemical, biological transformations as well as interactions with other biocomponents in the fluids of the GIT.

Efflux transporters: Efflux transporters reduce the BA of small compounds and form a significant biological barrier to the absorption and distribution of molecules. These are proteins transporters that are found on the membrane and transport molecules

out of cells, thereby, decrease their absorption and alter the pharmacokinetic properties (Seelig, 2020).

Enzymatic metabolism: An important factor in determining BA is metabolic enzymes. For substances that are taken orally and go through first-pass metabolism in the liver and intestines before entering the bloodstream, this component is very important. At the forefront of drug metabolism, cytochrome P450 (CYP) enzymes are in charge of the oxidative biotransformation of a wide variety of small compounds (Jager et al., 2014).

Inter-individual variability: Additionally, the impact of gut microbiota on BA varies significantly from person to person and is affected by various factors. These differences are caused by dietary habits, underlying disease conditions, age-related changes in the composition of the microbiome, past exposure to antibiotics, and genetic variables that influence the host-microbiome relationship (Wu et al., 2024).

Formulation and Delivery Challenges

Poor water solubility and low membrane permeability: Since oral drug administration is non-invasive, simple to dose, economical, and highly patient-complied with, it continues to be the recommended method of drug delivery (Khan et al., 2022).

However, two physicochemical characteristics; intestinal permeability and water solubility, have a significant impact on the effectiveness and BA of medications administered orally. While sufficient permeability guarantees transport through the membranes, the dissolved form of the active pharmaceutical ingredient (API) is necessary for uptake from the gastrointestinal tract (GI) (Cascone et al., 2016).

Food-drug interaction: Drugs administered orally may come into contact with food (such as proteins, carbs, and fats), which can alter the absorption of the drug through a variety of mechanisms, including altering the time it takes for the stomach to empty, the pH and duration of the drug's residence in the GIT, the hepatic blood flow, and by modifying efflux transporters and presystemic metabolism. The combination of grapefruit juice and nifedipine is one of the traditional pharmacokinetic interactions of dietary ingredients with medications (Mouly et al., 2017).

Drug interactions with herbal substances and vitamin supplements:

The Food and Drug Administration (FDA) defines food-drug interactions (FDIs) as alterations in a medicine or pharmacokinetic or pharmacodynamic characteristics of nutrients, or a reduction in nutritional status brought on by the administration of a pharmacological agent (Gouws & Hamman, 2020). Herb-drug interactions (HDIs) are interactions between the drug and the constituents of herbs that can also result in such effects. These relationships affect the drug's efficacy and safety by either enhancing or decreasing its therapeutic effect, which makes them clinically significant. Interactions between food and herbal substances can alter drug concentrations in the blood by affecting the transporters and enzymes involved in drug metabolism. These changes can directly affect the safety and efficacy of the treatment (Koziolek et al., 2019).

STRATEGIES TO ENHANCE BIOAVAILABILITY

Various strategies including formulation-based approaches, chemical modification and others, have been formulated or investigated to enhance the BA of natural compounds. Fig. 2 demonstrates various strategies to enhance BA of natural compounds.

Formulation Based Approaches

Nanoparticles based formulation:

The incorporation of nanoparticles to enhance the BA of natural compounds has been found to be an innovative approach as the size of drug particles affects pharmaceutical absorption. (Hoogevest et al., 2013). In recent years, Nanoparticulate drug delivery systems (NDDS) have attracted more attention as they can provide better drug absorption, enhance intracellular delivery, and prevent premature drug breakdown and interaction with the physiological environment. In oral administration of different drugs, many NDDS including, liposomes, solid-lipid nanoparticles (SLNs), polymeric micelles (Wang et al., 2020). Table 1 demonstrates

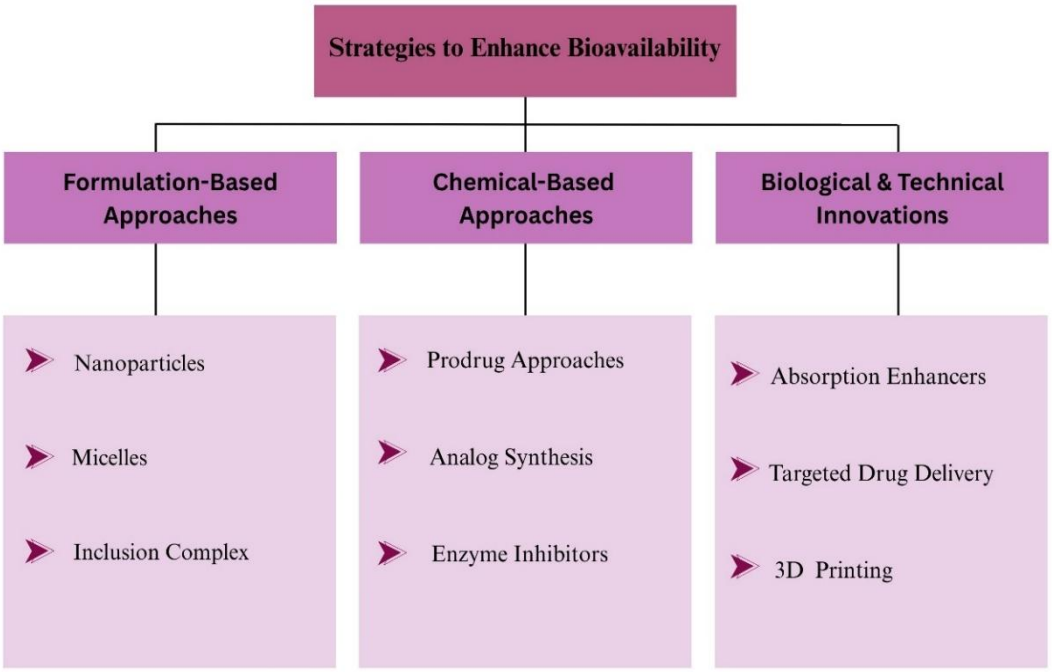

Fig 2. Different strategies to enhance bioavailability of natural compounds

the nanoparticle-based formulations to enhance the BA of natural compounds.

Other Formulation-Based Approaches

Self-emulsifying drug delivery system (SEDDDS): Alternatively, SEDDS systems produce emulsions with droplets between 100 and 300 nm in size (Gursoy et al., 2003). The self-emulsifying systems may trap 100% of the drugs and also work well in producing physically stable (they also can be contained in the capsules) submicron droplets which enhance the extent of the drug absorption accompanying with the increased surface area together with the BA (Mahmoud et al., 2009).

Inclusion Complex

Cyclodextrins (CDs): Enzymes convert starch into cyclodextrins, which are capable of forming inclusion complexes. By absorbing an entire drug molecule or a portion of it into the cavity, CDs can form inclusion complexes with a variety of medications. Various physicochemical characters of medications, primarily their rate of dissolution and water solubility, will be impacted by this type of molecular encapsulation. Among the different strategies, making inclusion complexes with CDs has been proven to be effective in increasing the solubility of natural products that are not very soluble in water (Viswanathan et al., 2019).

Chemical Modification to Enhance Bioavailability

Prodrug approaches and analog synthesis: A prodrug is often characterized as an inactive or physiologically inert molecule that will be chemically or enzymatically activated within the human body but lacks pharmacological characteristics. Prodrugs enhance the chemical characteristics of active medications, increasing their BA and lowering the possibility of metabolic interference, by adding pharmacologically inert moieties for instance, phosphates, esters, and amides (He et al., 2024).

Analog synthesis: Compounds that are chemically altered to improve specific properties while maintaining the biological action of the parent medicine are known as drug analogues (Das et al., 2022). Analogue synthesis involves changing the molecular weight, shape, designing prodrugs and structurally modifying them to improve hydrophilicity and lipophilicity. It is well accepted that natural active compounds are excellent sources for finding structurally novel lead compounds. The potential of natural product resources can be tapped

and the chances of developing new drugs increased by creating various analogs of natural products through molecular or structural modification and optimization. These methods enhance PK properties and allow the investigation of structural changes (Singh et al., 2023).

Enzyme inhibitors: Both naturally occurring and artificially design enzyme inhibitors are used to enhance BA of natural compounds. By inhibiting the transporters involved in molecular disposal and metabolic enzymes (enzyme inhibition), these inhibitors increase BA. Pharmaceutical companies employ enzyme inhibitors including, alpha-glucosidase inhibitors (AGIs) and carbonic anhydrase inhibitors (CAIs) most frequently to treat pathological disorders by targeting human enzymes (Prete & Pagano, 2024).

Biological and Technology Innovation

Absorption enhancer: The goal of biological and biopharmaceutical approaches is to improve drug absorption and combat physiological obstacles. Enzyme inhibitors and permeability enhancers are used to overcome intestinal efflux and first-pass metabolism, increasing systemic drug circulation (Gomez-Orellana, 2005). Bioenhancers can increase the BA of drug molecules through three main mechanisms; active efflux transporter modulation, including P-gp-related efflux inhibition; tight junction modulation to increase paracellular diffusion; and modification of plasma membrane fluidity to increase passive transcellular drug permeation. Drugs that are substrates of CYP enzymes can have their BA greatly impacted by inhibition of these enzymes in the liver and intestinal epithelium, which lowers pre-systemic metabolism (Kumar-Sarangi et al., 2018).

Ligand-based targeting: Ligand-based targeting is another practical strategy to increase the BA of natural substances. Either a direct linkage (chemical or biological conjugation) or an indirect coupling, which includes a carrier that contains the medication and displays the targeted ligand, can be helpful. This approach can increase the absorption of natural compounds well as reduce the harmful effects of several chemotherapeutic medications that can attack healthy cells (Muro, 2012).

3D printing: A new method called 3D bioprinting uses computer-aided design (CAD) software to generate a digital model of the desired structure, which a 3D printer then uses to turn it into a tangible product. To produce a three-dimensional structure that resembles the original tissue, the printer subsequently applies layers of bioink, which is made up of living cells and other biomaterials. By adjusting internal geometries and materials, 3D printing enables the production of personalized tablets with accurate release profiles. Tablets with controlled release profiles, such as immediate, sustained, or delayed release, can be produced using processes including, selective laser sintering (SLS) and fused deposition modelling (FDM), which enables better absorption and prevents the degradation of compounds, thus increasing their therapeutic efficacy (Patel, 2011).

CASE STUDIES OF NATURAL COMPOUNDS AND THEIR PK PROFILES

Curcumin-Low Bioavailability and Approaches to Enhance Absorption

Curcumin, a bioactive ingredient of turmeric, or *Curcuma longa* L., has shown effectiveness in treating a number of diseases, including immunological deficits, cancer, cardiovascular disease, diabetes, Crohn's disease, Alzheimer's disease and arthritis (Anand et al., 2007). Despite its proven therapeutic effects, curcumin's weak solubility, low gut absorption and quick systemic clearance restrict its potential health advantages. Limited plasma levels, low permeability, rapid metabolism, and excretion from the body are some of the variables that contribute to its limited BA. Although, curcumin's poor systemic BA and limited absorption hinder its application in clinical settings, there are various strategies to improve absorption and reach a therapeutic dose of curcumin (Jager et al., 2014).

Many strategies, such as nanogels, nanocrystals, liposomes, emulsions, and self-assemblies have been used recently to increase curcumin absorption (Yallapu et al., 2012). Similarly, it has been demonstrated that the incorporation of curcumin into phospholipid complexes and curcumin supplemented with a micellar surfactant (polysorbate) increases absorption by 3.4 and 9.0 times, respectively (Yu & Huang, 2012). It has been

demonstrated that a microemulsion system containing curcumin and a mix of nanoparticles of polylactic-co-glycolic acid (PLGA) and PLGA-polyethylene glycol (PEG) increases the relative absorption of curcumin in rats (Hu et al., 2012). In addition, food-grade formulations have been demonstrated to increase the amount of curcumin in the blood by 27.6 times. These formulations contain curcuminoids and volatile oils of turmeric rhizome (CTR), as well as a mixture of curcumin, glycerin, gum ghatti, and water. The preparation process involves wet milling, followed by dispersion using high-pressure homogenization (Sasaki et al., 2011).

Resveratrol (RSV)-Metabolism and Strategies for Improved Systemic Exposure

RSV, a polyphenolic molecule, has been shown in several in vitro experiments to have a variety of pharmacological effects, including antioxidative, anti-inflammatory, anti-obesity, and estrogenic effects, as well as anticancer and chemoprotective actions (Springer & Moco, 2019). However, numerous studies have shown several problems with resveratrol, including its quick and broad first pass metabolism and enterohepatic recirculation, that are responsible for its low systemic BA (almost zero) (Summerlin et al., 2015; Francioso et al., 2014). So far, various approaches have been used to increase resveratrol's BA and cellular absorption including, nanostructured delivery systems and resveratrol prodrugs (Singh & Pai, 2014). Researchers have made efforts to formulate RSV derivatives with increased BA and stronger biological activity by hydroxylation, amination / amidation / imination, methylation, prenylation, halogenation, oligomerization, and glycosylation (De Amicis et al., 2011). Additionally, researchers have been using nanotechnology to coat RSV, which has been demonstrated to improve BA by making it more soluble in intestinal fluids, enabling enterocyte absorption and lowering metabolism prior to absorption. RSV can be encapsulated with a broad selection of delivery technologies including, liposomes, nanoemulsions, niosomes, dendrimers and nanoparticles (Chopra et al., 2022).

Quercetin, Berberine and EGCG – PK Challenges and Recent Innovations

Quercetin is a flavonoid compound known to possess many therapeutic properties however, its potential uses are limited by its poor BA. Various nanocarriers have been developed to overcome this challenge and increase the concentration of quercetin at the target site by improving its BA (Pinheiro et al., 2021). Another, natural compound, berberine (BBR), a benzylisoquinoline alkaloid, with a variety of pharmacological actions is used worldwide to treat numerous diseases (Kong et al., 2022). However, rapid metabolism, systemic clearance and limited absorption, is known to limit its BA in the body. To address this problem and improve its BA, researchers are now working on a number of strategies, including the development of structural analogues of berberine, microemulsions, and novel drug delivery systems (NDDS) (Thomas et al., 2021). Similarly, epigallocatechin gallate (EGCG), the main catechin in green tea, is prone to decreased stability, decreased BA, and a reduced absorption rate because of a variety of environmental, formulation, processing, and gastrointestinal factors. To address the barriers to EGCG ingestion, new prodrug strategies, glycosylation methodologies, and a few new nanoparticle methods have been developed (Mehmood et al., 2022). Table 2 presents case studies of some natural compounds.

EMERGING TRENDS AND FUTURE DIRECTION

The application of predictive modeling in PK has changed a great deal in that we have moved from classical in silico simulations towards something much more personalized in relation to the characteristics of an individual patient. Advanced computer technology has facilitated the development of intricate models. These models analyze drug behavior in diverse demographics, considering factors such as age, weight, and sex. Subsequently, they are used to optimize treatment regimens. To investigate the ligand-binding affinity, and the behavior of drugs in biological systems, the in-silico simulations such as molecular docking and molecular dynamics have proven to be essential in achieving the optimal potency of a drug dosage (Paliwal et al., 2024). Similarly, artificial intelligence (AI) approaches offer novel insights and new instruments to predict the performance and

safety of therapeutics, improve patient outcomes, and maximize drug dose (Pawar et al., 2021).

Beyond these technological developments, PK has extended our understanding of inter-individual differences in drug response. The human microbiome is important to drug metabolism and therefore influences the effectiveness and toxicity of pharmacological treatment. In recent years, pharmacomicrobiomics has elucidated the role of the gut microbiota in influencing drug absorption, metabolism, and excretion, which results in inter-individual variations in treatment response. The complex interaction of the microbial community and drug metabolism provides new opportunities in individualized drug treatment and precision medicine. A paradigm change for precision medicine might be imminent with the development of pharmacomicrobiomics and the incorporation of microbiome data into therapeutic decision-making (Dzobo, 2022).

In addition to these developments, pharmaceutical companies still face substantial obstacles due to low solubility, which is now regarded as a critical challenge for biomedical research. The implication of the novel lipid-based nanocarriers and nanomaterials e.g., dendrimers and carbon nanotubes as delivery system, has proven an efficient measure enhancing drug BA through crossing the barrier and addresses all concerns with solubility and BA. (Beg et al., 2011). Nevertheless, such innovations must consider the regulatory aspects needed to achieve products that are safe, effective and consistent. In this regard, various regulatory agencies including, WHO, EMA, and AYUSH have developed guidelines on the production, labeling, and marketing of nature products, making laws more standardized and uniform globally (Wang & Grainger, 2022).

All these innovations, combined with the concept of precision medicine have been transforming the healthcare sector by adjusting diagnostics and therapies to the unique and constantly changing health condition of individual patients (Dzobo, 2022). Pharmacometrics, the combination of pharmacokinetic (PK) and pharmacodynamic (PD), and mathematical models serve to optimize and predict drug behavior and identify drug-drug interactions. Moreover, combining large data volumes in computation tools, electronic health records (EHRs) and omics data are some of the avenues that can help gain meaningful information in this sector. Despite their relatively recent introduction, machine learning (ML) algorithms and artificial intelligence (AI) methods also serve as tools to study big data and build predictive models that could be used by scholars. Similarly, new in silico methods promise to revolutionize medicine for future generations (Marques et al., 2024).

CONCLUSION

Natural compounds possess enormous therapeutic potential however, they have poor PK and low BA, which limit their clinical success. To maximize their potential, the knowledge of the ADME properties and overcoming the barriers to absorption and metabolism should be considered. The chapter has highlighted various BA enhancement strategies including, chemical modifications, new formulations as well as emerging tools i.e., AI and personalized PK. In the near future, a combination of these approaches will be highly beneficial to the development, standardization and therapeutic success of natural products in modern medicine.

Table 1. Nanoparticle-based formulations to improve the bioavailability of natural compounds

Nanoparticles based formulation	Composition	Mechanism of Enhance Bioavailability	References
Liposomes	Hollow shape, spherical encapsulated in lipid membrane	Target release, improve drug stability	Hoogevest et al., 2013
Solid lipid nanoparticles	Solid lipid core stabilized by emulsifiers	Prevent pre-systematic hepatic metabolism, enhance bioavailability	Manjunath & Venkateswarlu, 2005
Micelles	amphiphilic molecules consisting of hydrophobic cores and hydrophilic capsules	carry hydrophobic drugs in the core, enhance dissolution	Viswanathan et al., 2019

Table 2. Case studies of some natural compounds, representing issues to their bioavailability, strategies to cope with these challenges, and possible outcomes

Compound	Challenges to Bioavailability	Strategies	Outcomes	Citation
Curcumin	Low solubility, rapid metabolism	Nanoparticles, emulsions, Food-based combination	Increase Absorption	Yallapu et al., 2012
Resveratrol (RSV)	Rapid metabolism	Nanostructured delivery systems, prodrugs, RSV derivatives	Enhance Systematic exposure	Chopra et al., 2022
Quercetin	Low permeability	Nanoparticles i.e, lipsosomes, cyclodextrins	Improve Bioavailability	Pinheiro et al., 2021
Berberine	quick metabolism, limited absorption,	analog synthesis micoemulsions, and novel drug delivery systems (NDDS)	Increase Absorption	Thomas et al., 2021
Epigallocatechin gallate (EGCG)	Degradation, limited absorption	Nanoparticles, prodrugs formulations	Enhance Bioavailability	Mehmood et al., 2022

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