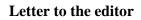
# Zagazig Journal of Pharmaceutical Sciences

Journal homepage: https://zjps.journals.ekb.eg/

Print ISSN: 1110-5089 Online ISSN: 2356-9786



جامعة الزقازيق

### **Redefining Bioavailability to Accurately Predict Intracellular Therapeutic Targeting**

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#### ARTICLE INFO

#### ABSTRACT

Article History: Received: 26 Nov 2024 Accepted: 4 Dec 2024 Published online: 31 Dec 2024

Key words: Bioavailability, intracellular infections, COVID-19, drug delivery, and pharmacokinetics The COVID-19 pandemic, coupled with ongoing challenges in the development of effective anticancer therapies, has underscored critical limitations in the traditional understanding of bioavailability. Historically, the concept of bioavailability has been narrowly defined, focusing primarily on systemic absorption and the subsequent distribution of drugs to tissues. However, this perspective fails to account for the complexities of how drugs access specific intracellular targets. In this letter to the editor, we advocate for the introduction of a more comprehensive definition of bioavailability, one that considers not only the absorption and tissue access of a drug but also the speed and extent to which a biologically active molecule reaches its intended intracellular site of action. We propose that, in addition to absorption, other key factors such as protein binding, cellular penetration, metabolic stability, and the activity of efflux pumps should be incorporated into the bioavailability framework. These factors play a pivotal role in determining drug efficacy, particularly in the treatment of intracellular infections or disorders involving specific cellular targets. By expanding the definition of bioavailability in this way, we can better address the challenges of drug development and enhance the precision of therapeutic interventions that require targeted intracellular delivery.

### 1. Introduction

The conventional definition of bioavailability as "the rate and extent of drug absorption" [1] oversimplifies drug effectiveness by neglecting critical factors influencing interactions with intracellular targets. A more precise definition was proposed as "the extent and rate to which the active drug becomes available at the site of action [2].

### 2. COVID-19 Pandemic:

The COVID-19 pandemic exposes the limitations of the traditional understanding of bioavailability, to predict efficacy in the management of intracellular viral infections like SARS-CoV-2. Notably, drugs such as lopinavir/ritonavir and hydroxychloroquine,



despite having >80% systemic bioavailability and promising in vitro efficacy, encounter barriers to accessing target cells, limiting their effectiveness in clinical settings. Similarly, remdesivir with 100% systemic bioavailability faces challenges due to rapid metabolism [3].

# 3. Anticancer drugs:

In the context of anticancer treatment, the efflux pump P-glycoprotein (P-gp) plays a pivotal role in mediating multidrug resistance (MDR) by actively reducing intracellular concentrations of chemotherapeutic agents such as paclitaxel. This resistance mechanism is particularly detrimental in advanced breast cancer (ABC), where elevated P-gp expression prevents effective oxidative stressinduced damage to cellular and mitochondrial membranes, thereby impairing therapeutic efficacy. Targeted strategies to overcome MDR have focused on nanocarriers capable of co-delivering P-gp inhibitors and anticancer drugs [4].

## 4. Redefinition of Bioavailability:

To address existing challenges, we redefine bioavailability as the "rate and extent at which a drug reaches its extracellular or intracellular specific sites of action within target organs or cells." This expanded definition accounts for critical factors beyond systemic absorption, such as strong protein binding, sufficient lipophilicity for intracellular penetration, and metabolic stability. These considerations are essential for accurately predicting drug efficacy in clinical settings[5-7].

## 5. Implications:

The redefined concept of bioavailability has significant implications, shaping the development of innovative drug delivery systems and target-specific therapies to address intracellular barriers. It facilitates a more thorough evaluation of drug candidates with enhanced intracellular bioavailability profiles. This approach allows for tailored treatment regimens based on individual pharmacokinetics and potential barriers.

## 6. Conclusion:

Redefining bioavailability to encompass cellular and target-specific aspects represents a paradigm shift in

understanding drug efficacy against intracellular infections or pathophysiological diseases. This broader perspective holds immense potential for advancing research, drug development, and ultimately improving therapeutic outcomes for these challenging diseases.

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