Multidrug Resistance: Clinical Significance and Solutions

Babak Fozooni Moqadam[1], Lia Tsiklauri[2]

[1]BA student, 4th semester, Pharmacy English Program, The University of Georgia, School of Health Sciences and Public Health, Georgia;
[2]Supervisor, PhD, Senior Researcher, I. Kutateladze Institute of Pharmacochemistry, TSMU, Georgia

Multidrug resistance (MDR) is a remarkable problem in the therapy of several disorders. MDR is a phenomenon when cells become resistant to diverse pharmacologically active compounds with structural and functional differences. Numerous mechanisms for MDR have been suggested, including enhanced drug efflux due to ABC-transporter protein overexpression. Consequently, the development of ABC-transporter modulators has been supposed rational approaches for overcoming MDR.
The searches of scientific literature were performed in PubMed/MEDLINE, and Google Scholar databases to choose studies that examined the effect of MDR on clinical results and attempts to address this phenomenon. All retrieved papers were analyzed and those considered relevant for the purpose were included.
In almost all disorders, the MDR phenotype plays a key role in treatment ineffectiveness. It is a characteristic found in all living things, from microorganisms to humans. Several mechanisms of MDR, such as enzymatic degradation, attachment site mutation, down-regulation of outer membrane proteins and efflux pumps have been proposed. MDR membrane proteins (ABC-transporter) are important regulators of drug resistance since they efflux a variety of substrates across the cell membrane versus a concentration gradient using energy derived from ATP hydrolysis to ADP. MDR-ABC-transporters are unique because they recognize specific chemical substrates and extract them into the extracellular milieu. These efflux transporters lower intracellular concentrations of drug and impair drug response, limiting successful therapy. Many of these transporters play an essential role in tissue defense and are found primarily in the kidney, pancreas, liver, gastrointestinal tract, and testes and brain endothelium vessels. After the detection of the critical function of ABC-transporter overexpression in MDR, researchers have focused their efforts on finding drugs that can antagonize or inactivate these transporters in order to overcome drug resistance. Numerous MDR inhibitors have been identified, but none of them have been manifested clinically useful without side effects. Compared with conventional methods, nanotechnology provides an innovative and promising alternative strategyto reduce drug resistance. Nanotechnology-based co-delivery techniques possess great advantages for site-specifying targeting, controlled drug release, and identical drug PK profiles.
Nanoparticles are widely developing in an effort to overcome MDR. Nanocarriers have effectively overcome the problem of poor intracellular concentration, lack of targeting tissues and low bioavailability.

Keywords: multidrug resistance, drug efflux, MDR inhibitors, nanocarriers.

Abbreviations: Adenosine diphosphate (ADP), ATP-binding cassette (ABC), Multidrug resistance (MDR), Pharmacokinetics (PK).