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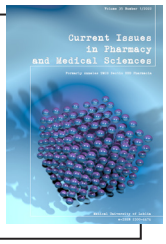

Natural bio-enhancer for bioavailability enhancement

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ABSTRACT

There is a connection between bioavailability and absorption. In the field of pharmacology, this is referred to as a category of absorption and is defined as the proportion of a particular dosage of a drug that does not change and is absorbed into the systemic circulation. Both the overall absorption of medications and their specific bioavailability are important factors to consider in treatment. In this paper, we will go into great detail about the bioavailability of phytochemicals. We will also discuss the factors that influence bioavailability, the processes that improve bioavailability, and the phytochemicals that act as important bio enhancers, which are agents that improve the bioavailability of drugs.

INTRODUCTION

The percentage of a drug that really makes it to the tissues or cells that the drug was designed to affect is referred to as the drug's 'bioavailability', and it is defined as the amount of the drug that actually reaches its intended target areas [1-3]. It is essential to have a solid understanding of the various routes of drug administration in order to have a firm grasp on bioavailability. Drugs can be administered orally, sometimes by placing something underneath the tongue, sometimes by dropping them in the eye, ear, or nose, and occasionally by inserting something in the rectum or vagina [4-6]. It is also possible to deliver certain medications to the lungs by inhaling them. The injectable method is the most effective; depending on the desired impact, a medicine may be injected into the vein, the muscle, the skin, or the space between the vertebrae (intrathecally). In order to obtain a systemic impact with some medications, it is sometimes necessary to apply them in the form of a patch. Drugs can be taken orally in the form of liquid, capsules, pills, or suppositories, which are put into the vaginal or rectal cavity and work similarly. When they are dissolved, drugs that are in solid form can have a local or systemic effect. Inhalation is the mode of delivery for a few different types of medications. These medications are atomized into very little amounts; the smaller the drops, the greater the depth to which they can travel. Figure 1 illustrates a number of distinct approaches to the administration of drugs [7-10].

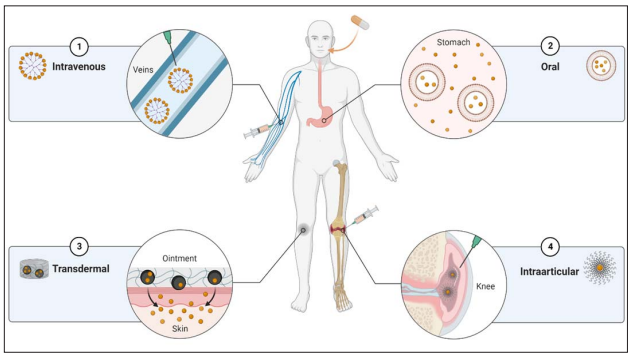

Figure 1. Different modes of drugs administration

Within a human body, the concentration of a drug will decrease as time passes. When a medicine is taken orally, it first travels to the stomach, where it is dissolved, and then some of it is absorbed into the blood. After there, it travels to the small intestine, which is the final stage of the absorption process. It is possible that the bioavailability is low since digestion in the stomach and small intestine is not very efficient. After being taken in by the body, medicines are transported to the liver via the hepatic vein. First-pass metabolism is the process that takes place in the liver when drugs are broken down [11,12]. Oral administration of a drug is the most effective method of therapy because it is not

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only simple and hassle-free, but it also eliminates the need for painful injections. However, when the oral medication is not effective, the intravenous form of the medication is frequently used instead. Systemic circulation and pulmonary circulation are both counted as components of the circulatory system. Drugs, once they have broken through the biological cell membranes, are transported by the systemic circulation to the locations where they are needed [13,14]. The letter 'f' represents the degree to which bioavailability can be measured. Because the injection of a drug intravenously produces the best results, this method defines the substance's absolute bioavailability. After being administered through vein injection, the medication enters the bloodstream, travels to its destination, and takes effect there [15]. The term 'Tmax' refers to the point in time at which the maximum concentration of a medication may be detected in the blood, whereas 'Cmax' refers to the highest concentration of the drug that can be discovered in the blood. It is possible that some of the substance that has been supplied will be digested and then eliminated from our bodies while it is still moving through our bloodstream. Even if taking a drug by mouth is the most practical method, doing so frequently results in a reduction in the drug's bioavailability. In order for a molecule of a medicine to be effective, it has to be bioavailable, and in order for molecules to be bioavailable, they need to be able to pass through the gastrointestinal (GI) membrane. Another phrase that is commonly used in connection with the process of drug absorption in the body is 'bioequivalence' [16]. In pharmacokinetics, the concept of bioequivalence is utilised to determine whether or not two medications have comparable levels of bioavailability. When it comes to their level of effectiveness, two medications that are bioequivalent need to be on par with one another. It is therefore a comparison of two medications, and it may give an indication as to which one may be substituted for the other.

Factors affecting bioavailability

There are inter-individual variations among patients, and sometimes, the same patient may show different characteristics at different times [17]. The pH of the GI fluid, interactions with other medications, diet, and other factors all affect a drug's bioavailability. As was previously said, there are additional ways to administer medication to a person. Administration through the nose is neither intrusive nor painful. Drugs can easily enter the nasal cavity due to the porous epithelial surface. This approach can be used with medications intended for the nose and brain. These medications can avoid the liver's first-pass metabolism if administered through the nasal cavity [18]. Drugs can also be administered intravenously, intramuscularly, subcutaneously, or intrathecally – that is, around the spinal cord. The most efficient method of drug administration is intravenous. As suppository, drugs can also be administered through the rectum. Drugs are administered this way when treating nausea [19,20].

Improvements in bioavailability

Pharmacology's current problem is improving bioavailability. The main problems that impede many pharmacological compounds' initial development are their poor bioavailability and poor solubility in water. A number of strategies have been devised to increase these drugs' aqueous solubility and dissolution rates, hence enhancing their oral bioavailability. Salt production and the use of solubilizing chemicals are common techniques to speed up drug breakdown. These techniques, meanwhile, have certain drawbacks [19]. Salt formation could have negative repercussions. Problems could arise if another solvent is added. The addition of liposomes, emulsions, and microemulsions, however, may improve bioavailability. Moreover, drugs are increasingly being reduced to submicron sizes, a process known as 'nanosizing'. A medication needs to be dissolved before diffusion. Therefore, the solubility in the gut is a key factor. Reduced drug particle size increases the likelihood of contact with the solvent, which increases the likelihood of improved solubility. Therefore, improving a drug's solubility may be the best strategy for boosting bioavailability. Poorly bioavailable medications are never able to exert their full potential. The dose only partially reaches the target organ through circulation. In order to compensate for the drug's poor bioavailability, a very high dose must be given, and serious side effects can be brought on by the drug's extremely high dosage [20]. Danazol is one medication used to treat endometriosis. Danazol is administered in extremely high doses due to its limited bioavailability. This has a number of negative impacts. Additionally, giving patients a prescription for such a large amount is expensive for them. Therefore, improvement of bioavailability of a drug is of enormous importance. Poorly absorbed drugs may be made bioavailable, employing a number of approaches:

- Using enhancers that increase absorption and hence bioavailability;
- Using pro-drugs;
- Pharmaceutical approaches, i.e., drug delivery systems;
- Using P-gp inhibitors.

Using enhancers that increase absorption

Drug absorption in the gut may be aided by bile salts, surfactants, chelating agents, polymers, fatty acids, and other substances. There is also chitosan. These all work to make hydrophobic medicines more soluble. By lowering calcium levels, calcium chelators like EGTA and EDTA improve absorption.

Prodrug

Drugs are frequently found in pro-drug form. These pro-drugs are covalently joined to a drug, altering the physicochemical properties, to increase bioavailability. The covalent bond is constructed in such a way that it can be easily broken, releasing the active medication. The circulatory system absorbs the pro-drug. These pro-drugs are occasionally not very soluble. Nonpolar moieties that cover the pro-drug are another drawback. In that situation, the drug builds up inside the cell, where the pro-drug undergoes biotransformation to become an active drug. Through the use of an ester bond, highly charged molecules like phosphate and carboxyl groups are concealed by nonpolar groups, increasing the drug's permeability and lipophilicity. Ester

bonds are relatively easily broken. Pro-drugs may occasionally be employed to boost transporter activity. Here, the linked moiety serves as a place where the transporter proteins can be recognised. Bioavailability is also enhanced by bile acid transporters. The effectiveness of the medicine is determined by the attachment location and the size of the drug. In addition to enhancing bioavailability, pro-drugs can deliver long-acting pharmacological characteristics. In this approach, the medications' half-life can be extended [19-21].

Pharmaceutical Approaches

It is possible to improve the intestinal absorption of medications by using dosage forms that can increase the permeability of the intestinal wall. This is a very effective method. These formulations are emulsions and liposomes, both of which increase the amount of substance absorbed by the intestinal tract. Another alternative would be to lessen the magnitude of the drug's individual particles. When we talk about reducing particle size, we are referring to processes like micronization and the use of nanoparticular carriers, all of which can help with drug absorption. The process of nanosizing will be covered in greater depth later [21,22].

Inhibition of P-gp

P-glycoprotein 1, also known as 'MDR1' or 'ATP binding cassette subfamily B member 1', is a type of protein that confers resistance to many drugs (ABCB1). This is a very vital protein that acts like a pump in a cell, removing any harmful or undesired chemicals from the body. This protein is stopped in its tracks by phytochemicals that perform the role of bio enhancers. Inhibition of the substrate P-gp by bio enhancers can take place in a number of different ways. These include acting as a competitive inhibitor, an uncompetitive inhibitor, a non-competitive inhibitor, or an irreversible inhibitor. These inhibitors put a stop to the active transport of drugs. As a direct result of this, there is an increase in the bioavailability of the medicine in the gut. The ABCB1 gene is responsible for encoding this glycoprotein. Because P-gp is responsible for the normal elimination of xenobiotics, these substances are returned to the gut lumen. As a result, the effectiveness of certain pharmaceutical medications is diminished. These pharmaceuticals are thought to act as substrates for P-gp. Cancer cells tend to have high levels of P-gp expression. As a result of this, cancer cells develop resistance to many drugs. P-gp plays an important role in the transport of many different medications, including a number of anticancer drugs such as etoposide, doxorubicin, vinblastine, gefitinib, sunitinib, and many others. Some more medications that are carried by P-gp include cardiac glycosides like digoxin and glucocorticoids like dexamethasone. P-gp efflux brings the concentration of medications inside the cell down to a level where they are no longer effective for therapeutic purposes. Through their interactions with the promoter region of the P-gp gene, some transcriptional factors such as p53 and NF-B are able to control P-gp expression [15,24].

Enhancement of bioavailability

As stated previously, there are a few different ways that a patient's prescribed medications might be administered. However, in order to improve the drug's systemic bioavailability, it can also be administered by the parenteral, nasal, vaginal, rectal, or transdermal routes in addition to the oral route, which is the most popular and easiest to use. However, from a practical standpoint, it is always preferable to work toward increasing the oral bioavailability of the medicine [14,15,24].

Details of techniques that improve bioavailability

The pharmaceutical technique known as 'nanosizing' involves reducing the size of the medicine to that of a nanometer or smaller. The availability of medications that are taken orally is contingent upon their capacity for absorption in the digestive tract. The migration of the substance that has been provided from the place where it was administered into the circulatory system is referred to as 'absorption' [14,16].

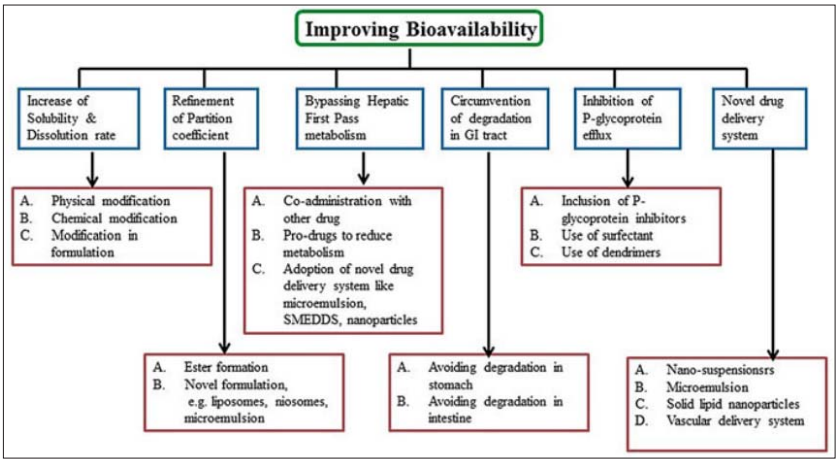

Figure 2. Different methods of bioavailability enhancement

In the top-down methodology, the decrease of size is accomplished by the utilisation of high-energy strategies. In order to carry out this method, homogenization under high pressure is necessary. In this method, each step is performed in a medium containing liquid, and the result is the formation of nanosuspensions. The distribution of the drug can be localised using bio adhesive delivery methods, which also allow for a slower rate of drug release. 'Bioadhesion' is the term used to describe the process of binding a natural or synthetic polymer to a biological system. This method of drug distribution is an effective strategy, especially when the compliance of the patient is taken into consideration. The drug transport mechanism is assisted by the plasma membrane protein known as 'P-glycoprotein' (P-gp) [24], which is also known as a multidrug resistant protein. P-gp is responsible for the expulsion of drugs from the cell. P-gp inhibitors have the potential to cause changes in the pharmacokinetics of a medication, for example, P-gp inhibitors raise the amount of a substrate that can be absorbed by the mouth. Some of the P-gp inhibitors include colchicine, felodipine, diltiazem, erythromycin, omeprazole,

ketoconazole, lansoprazole, and other proton-pump inhibitors, tamoxifen, nifedipine, quinidine, verapamil, etc [14,17,19].

Phytochemicals as enhancers of bioavailability

In *in vivo* models, many medications, even those that are herbal or derived from plants, are unable to demonstrate their entire potential. This is due to the insoluble nature of the medication in lipids and its relatively large size, both of which contribute to the drug's low bioavailability and absorption rates. Molecule originating from plants can be very effective in increasing bioavailability. As a result, it is essential to have an understanding of the enhancers of plant origin and the action mechanisms that they employ in order to boost bioavailability. In spite of the fact that they may have the ability to fight, for example, cancer, many of the compounds generated from plants are ineffective when tested in living subjects. This could be because of the molecule's large size, its poor solubility, or both. Because of these limitations, the absorption is weak, and as a result, the bioavailability is low. Due to their solubility in water, many phytochemicals are classified as phenolics. Because of this property, they are unable to pass through the lipid membranes that line the intestines and enter the body. There are particular plant products that have the potential to assist in enhancing bioavailability. Bose was the first person to uncover the action of a bioavailability enhancer in 1929. He detailed the effect of long pepper coupled with adhatoda vasaka leaves and documented the increased activity of vasaka. This was the first time the action of a bioavailability enhancer had been identified. In turn, an Indian researcher working at the Regional Research Laboratory in Jammu was the one who originally came up with the term 'bioavailability enhancer'. In 1979, this same researcher also identified and labelled piperine as the first enhancer of bioavailability [11-18].

CONCLUSION

In this review, we focused on phytochemicals and their functions as bioenhancers as we explored a variety of topics pertaining to bioavailability. We have discussed the numerous methods to evaluate bioavailability, the various elements that can affect bioavailability, the different strategies, such as nanosizing, that can improve bioavailability, and the roles that bio-enhancers play in increasing bioavailability. We have discussed the roles of different phytochemicals that act as bio-enhancers.There are several bioenhancers that function more effectively when combined with other enhancers. Because the bioenhancers boost the effectiveness of the pharmaceuticals, the required dosage of the drugs can be decreased, which reduces the associated toxicity and negative side effects. As a result of bioenhancers, therapies may become more efficient in terms of cost, as well as shorter in length and less likely to result in drug resistance.

AUTHORS' STATEMENT

We do not declare any conflict of interests that could affect the objectivity and credibility of the work.

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