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The Mechanism of Actions for Herbal Bioenhancers

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Abstract

Herbal bioenhancers do not possess their own inherent pharmacological activity, but when coadministered with other drugs, enhances their bioavailability and thus the efficacy. The interest for bioenhancers arises because of the chemotherapeutic agents which are poorly bioavailable and administered for prolonged periods, which can be toxic and expensive. One of the unique ways to achieve reduction in drug dosage and thereby drug toxicity and cost is to increase the bioavailability of drug. The present pharmaceutical research is more concerned with different aspects of exploring new chemical molecules having new modes of action. New drug development technologies were developed from the economics of treatment. There is a revolutionary shift in the way medicines are administered due to recent developments in enhancing the bioavailability. The present global focus is on methods aimed at reducing drug treatment period, leading to decrease in drug treatment cost. The reduction in cost of therapy will make the treatment more affordable for the financially challenged sections of the society.

Keywords: Bioenhancer, Bioavailability, Piperine, Niaziridin, Curcumin, Glycyrrhizin

Introduction

Bioavailability and bioefficacy of novel classes of drugs can be increased by herbal bioenhancers. In the today's era, there is a greater interest and larger healthcare need for the enhancement of bioavailability of many drugs which are less bioavailable. Poorly bioavailable drugs remain sub-therapeutic because a larger portion of dose never reaches the site of action to exert its biological effect. Thus, larger doses are required, which may lead to serious adverse effects. Improvement in bioavailability can result in lowering the dose and also the dose frequency of the drug.[1]

Being a developing country, cost of treatment is a real concern for new allopathic medicines in India. Innovative methods to reduce the cost of medicines are currently needed. Bioenhancers highlights the benefits of integrating ancient system with present modern system of medicine in practice. The complementary action of bioenhancer can reduce the dose of rifampin to half, thereby reducing the cost of treatment. This may lead to tremendous economic benefits for the world population suffering with tuberculosis. Also, if bioenhancer action is applied to other drugs, benefit levels can be astonishing. Internationally, billions of dollars are being spent annually due to the poor bioavailability of many drugs.[2]

The origin of concept of bioenhancers has given rise to a revolutionary shift in the way of treatment in therapeutics due to the advancement in bioavailability enhancing drugs. Recently, there has been an increase in the trend of sourcing the drugs from herbs by mankind because

of their lower risk benefit ratio in comparison to the newer allopathic medicines. Herbal bioenhancers have potential to enhance the bioavailability and bioefficacy of larger group of drugs, such as antiviral, antifungal, antibiotics, anticancerous and antituberculosis drugs. Indiscriminate use of antimicrobial agents causes multiple drug resistance. The patients need to consume excess amounts of antibiotics because of decreased absorption in gastrointestinal membrane, restricted uptake by target microbes and operation of efflux pump at the luminal membrane. Scientific researchers and pharmaceutical industries need to emphasize research to identify newer, better bioactive constituents from a wide array of unexploited herbs, having a role as a bioenhancer and bioefficacy facilitator. Scientists need to explore the actual mechanisms of action responsible for bioenhancing effects of bioenhancing molecules.[3]

Bioavailability is a measure of the steady rate and extent at which a biologically active substance enters systemic circulation. Oral administration yields non-consistent and incomplete drug absorption. The first pass metabolism degrades a portion of the drug before reaching the blood stream. The approaches of enhancing the bioavailability of a drug correspondingly increases drug levels in the systemic circulation and thus its efficacy. This in turn reduces the required drug dosage for achieving a particular therapeutic effect. Until now, physical methods namely micronization, timed/site release preparations, solubilisation of active drug and selection of crystal form and various methods of nanotechnology have been used for increasing drug bioavailability within a narrow manipulative framework.[4]

Novel Properties of Bioenhancers

- Most tolerable to humans or animals.
- Potent enough to show efficacy at low concentrations, when co-administered.
- Formulating the dosage should be easy.
- Most importantly, enhances bioavailability and bioefficacy of the drug molecules.[5]

The benefits of adding a bioenhancer includes decreased drug dosage, reduced cost of the drug, lesser incidence of drug resistance and lesser chances of adverse drug reactions/ side effects. Following the co-administration of bioenhancers, the drug dosage is reduced. Lower dose leads to reduction in drug resistance problems, especially in high toxicity causing therapy like anticancer drugs. This revolutionary discovery opened up a new field of increasing drug bioavailability.[6]

In the present new world, one can expect a revolutionary change in the way of therapeutics by enhancing the bioavailability of drugs using constituents of plant origin. Present review indicates that the pharmaceutical researchers have to emphasize on conducting experimental studies to isolate novel active phytoconstituents from a wide variety of unexplored herbs containing bioenhancer. Also, the need of the hour is to explore and identify the molecular mechanism of action by which these bioenhancer molecules exert their bioenhancing activity.[7]

The bioenhancers act by different mechanisms of action. Nutritional bioenhancers improve absorption by acting on gastrointestinal tract. Few bioenhancers mainly act by inhibiting the drug metabolism of antimicrobial agents. The following are various mechanisms of action postulated for herbal bioenhancers:[8]

- Augments the bioavailability of the drug across the gastrointestinal membrane
- The enzymes participating in metabolisms of drugs are inhibited and increases the total duration of action
- By conformational interaction and hence potentiating the drug action
- May act as self-receptor for any drug molecule
- Target cells of action are made to be more receptive to active drugs
- Inhibition of P-glycoprotein activity present on luminal membrane
- Attenuation of physical barrier such as an increase in intestinal brush border membrane fluidity
- Diminishing the secretion of gastric acid
- Enhancing gastrointestinal blood supply
- Gastric emptying time is reduced
- The intestinal motility is reduced
- Gastrointestinal epithelial cell membrane permeability modification
- Cholagogous effect
- Change in properties corresponding to thermogenic and bioenergetics
- Renal clearance inhibition by preventing the drug presence in glomerular filtration, reducing active tubular secretion by inhibition of P-glycoprotein and enhancing passive tubular reabsorption

- Inhibition of first pass metabolism
- Gamma glutamyl transpeptidase (GGT) activity is stimulated, which helps in uptake of amino acids
- Reduction in the dose of the drug due to immunomodulatory effect of the drug
- Penetration level is increased to such a high level that it can get access to even pathogen persistors within the macrophages, such as for *M. tuberculosis.* This process eventually ensures the elimination of these organisms from places otherwise less accessible to the active drug
- Altering the capability of pathogens or any abnormal tissues to reject the drug like efflux transporter mechanisms frequently encountered with antimicrobial, antimalarial and anticancer drugs
- The signalling process is modified between the host and pathogens leading to better accessibility of the drugs into the pathogens
- Better, improved binding of therapeutic drugs with the target sites like DNA, RNA, receptors, proteins, thus potentiating and prolonging its therapeutic effect against microorganisms

Advantage of Bioenhancers[9]

1. Bioenhancers reduce the therapeutic dose, narrows the treatment period
2. Reduces drug resistance problems
3. Due to dose- economy, they make treatment cost effective
4. The adverse or toxic reactions may be minimized[10]

At present, scientists are showing keen interest towards the improvement of bioavailability of huge number of drugs by addition of various herbs with bioenhancing properties. Active components of natural compounds with bioenhancing properties such as piperine, quercetin, genistein, naringin, niazeridine, lysergols, capmul, sinomenine, glycyrrhizin and nitrile glycoside are being isolated for their possible use along with modern medicines. Enhancement of bioavailability would

make many expensive drugs affordable and reduces the adverse effects by reducing the actual dose of the drugs. Also, the frequency of the dosage may be lowered.[11]

Medicinal plants containing bioenhancers:

- Piperine (*Piper nigrum*)
- Gingerol (*Zingiber officinale*)
- Capsaicin (*Capsicum annum*)
- Curcumin (*Curcuma longa*)
- Niaziridin (*Moringa oleifera*)
- Glycyrrhizin (*Glycyrrhiza glabra*)
- Black Cumin (*Cuminum cyminum*)
- Allicin (*Allium sativum*)
- Morning Glory Plant (*Ipomoea spp.*)
- Indian Aloe (*Aloe vera*)
- Caraway (*Carum carvi*)[12]

Future Perspectives

The bioenhancing concept is found to be very innovative in the modern era. In spite of the enormous beneficial effects of bioenhancers to the mankind, the job of exploring new herbal bioenhancers is still in nascent stages. There are still abundant bioenhancers of herbal origin that need to be explored in several vital areas. There is a huge range of untapped herbs which needs to be investigated for their bioenhancing effectiveness.[13]

Pharmaceutical corporations round the globe have continually been with the urge of discovering innovative blockbuster medicines for numerous ailments by outlay of billions of dollars for new drug discovery programmes. With the progress of new molecules, pharmaceutical science has gained a lot of success. However, the newly discovered molecules suffer various drawbacks such as poor aqueous solubility, lack of suitable bioavailability etc. The metabolism of API by cytochrome P450 in the gastrointestinal tract and within the liver is the major process which is responsible for diminishing bioavailability. Additionally, EDTs like P glycoprotein (P-gp), multidrug resistant associated protein (MRP) are also liable for reduced bioavailability of the therapeutically active medications, particularly metastatic tumour medications. Therefore, a certain alternative is needed by which the bioavailability of these drug molecules can be enhanced. The pharmacokinetic and pharmacodynamic profiles of these drugs can be modified by co-administration of these drugs along with bioenhancers.[14]

Conclusion

Bioenhancers comprises an innovative, novel concept as this invention is based on ancient and conventional structure of Indian medicine. One can expect complementary action of bioenhancers to lead to a

drop in treatment cost, toxicity, adverse effects and to have a valuable influence on the economy of the nation. Bioenhancers are found to be easily cultivated, procured, economical, non-addictive, safe, effective and have a wide range of applications.[15]

In developing countries like India, treatment expenditure is a key concern for modern medicines. Efficient novel means are the need of the hour for reducing the costs. The new drug development technique has been explored aiming the economics of treatment. As a result, treatments are now becoming more inexpensive for broad sections of civilization, including the economically challenged.[16]

The researchers now explore methods aiming at reduction of drug dosage and thus drug treatment costs, making the treatment affordable to a wider section of the society. The economic benefits will help poor patients needing prolonged and expensive antituberculosis, anticancer treatment. The main intension is to target expensive, toxic and scarce drugs or drugs that exhibit poor bioavailability.[17]

Conflicts of interest

None.

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