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Review

Role of herbal bioactives as a potential bioavailability enhancer for Active Pharmaceutical Ingredients

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ABSTRACT

The current review emphasizes on the herbal bioenhancers which themselves do not possess inherent pharmacological activity of their own but when co-administered with Active Pharmaceutical Ingredients (API), enhances their bioavailability and efficacy. Herbal bioenhancers play a crucial role in enhancing the bioavailability and bioefficacy of different classes of drugs, such as antihypertensives, anticancer, antiviral, antitubercular and antifungal drugs at low doses. This paper highlights various natural compounds that can be utilized as an efficient bioenhancer. Several herbal compounds including piperine, quercetin, genistein, naringin, sinomenine, curcumin, and glycyrrhizin have demonstrated capability to improve the pharmacokinetic parameters of several potent API. This article also focuses on various United States patents on herbal bioenhancers, which has proved to be beneficial in improving oral absorption of nutraceuticals like vitamins, minerals, amino acids and certain herbal compounds. The present paper also describes proposed mechanism of action, which mainly includes absorption process, drug metabolism, and action on drug target. The herbal bioenhancers are easily available, safe, free from side effects, minimizes drug toxicity, shortens the duration of treatment, lowers the drug resistance problems and minimizes the cost of treatment. Inspite of the fact that herbal bioenhancers provide an innovative concept for enhancing the bioavailability of several potent drugs, there are numerous bioenhancers of herbal origin that are yet to be explored in several vital areas. These bioenhancers must also be implied to enhance the bioavailability and bioefficacy through routes other than the oral route of drug delivery. There is a vast array of unexploited plants which can be investigated for their drug bioenhancing potency. The toxicity profiles of these herbal bioenhancers must not be overlooked. Researches must be carried out to solve these issues and to deliver a safe and effective dose of drugs to attain desired pharmacological response.

Contents

Abbreviations: P-gp, P-glycoprotein; CYP-3A4, cytochrome P450 3A4; AUC, area under plasma concentration curve; CVS, cardiac vascular system; CNS, central nervous system; BaP, benzo(a)pyrene; PIP, piperine; CUR, curcumin; MCF-7, Michigan Cancer Foundation-7

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1. Introduction

The practice of herbal medicines is carried out since centuries. There is a growing interest in improving the bioavailability of a large number of potent drugs by combining it with natural bioenhancers [1–3]. A bioenhancer is an agent which themselves do not possess inherent pharmacological activity of their own but when co-administered with the drug, enhances its bioavailability and efficacy. It was first time described by Bose in 1929 who reported the increased antiasthmatic potential of vasaka (*Adhatoda vasica*) leaves by combining long pepper with it. The concept of 'bioavailability enhancers' of natural origin has been obtained from the ancient knowledge of Ayurveda system of medicine. "Trikatu" is one of the ayurvedic preparations used from the period between 7th century B.C. and the 6th century A.D. for the treatment of a variety of ailments. It is a combination of black pepper (*Piper nigrum* Linn.), long pepper (*Piper longum* Linn.), and ginger (*Zingiber officinale* Rosc.), which contains active component piperine, which enhances the bioavailability of drugs, nutrients. Several drugs due to their low lipophilicity or zwitterionic character at physiological pH [4], or because of poor hydrophilicity or efflux by P-glycoprotein [5] are unable to cross the biological membranes. Therefore, the use of natural bioenhancers has gained importance in the current scenario to improve the pharmacokinetic parameters and hence bioavailability of various potent drugs [6,7]. The various mechanisms by which natural bioenhancers act are a) decrease in hydrochloric acid secretion and increase in gastrointestinal blood supply, b) hinder the gastrointestinal transit, gastric emptying time and intestinal motility [8], c) modifications in the permeability of the GIT epithelial cell membrane [9,10] d) cholagogous effect, e) bioenergetics and thermogenic properties [11] and f) suppression of first pass metabolism and inhibiting drug metabolizing enzymes and stimulation of the activity of gamma glutamyl transpeptidase (GGT) enzyme which enhances the uptake of amino acids [12,13]. They help in reducing the dose of drug, shorten the duration of treatment, lower the drug resistance problems, minimize drug toxicity and adverse reactions and reduce the cost of medicines. The various agents possessing the capability of enhancing the bioavailability of API are piperine, quercetin, naringin, glycyrrhizin, genistein, niaziridin, curcumin and sinomenine (Fig. 1).

2. The role of different natural compounds as drug bioavailability enhancers

2.1. Piperine

Piperine is a major plant alkaloid obtained from *P. nigrum* Linn (Black pepper) and *P. longum* Linn (Long pepper) [14]. Piperine is widely used as condiments and flavoring agent for all types of dishes, especially in India. In pharmaceutical field, piperine is known to possess anti-inflammatory activity [15,16], antipyretic activity [17], antifungal activity [18], antidiarrheal activity [8], antioxidant activity [19–23], antithyroid activity [24], antimutagenic activity [23,25–27], antitumor activity [26,28,29], antidepressant activity [30–32], analgesic activity, hepatoprotective activity [33], antihypertensive activity [34], etc. Piperine is scientifically validated as world's first bioavailability enhancer [11]. There may be two possible mechanisms by which piperine act as bioenhancers: (1) promoting rapid absorption of drugs and nutrients, and (2) inhibiting enzymes participating in biotransformation of drugs. It is a potent inhibitor of P-gp efflux transporter present in gastrointestinal wall and principal metabolizing enzyme CYP3A4.

The antigenotoxic effects of curcumin and piperine singly and together against Benzo(a)pyrene evoked DNA harm in lungs and liver of mice were investigated by Sehgal et al. Benzo(a) pyrene (BaP) is one of the polycyclic aromatic hydrocarbons (PAHs) classified as carcinogenic to humans. Administration of BaP elevates the level of oxidative DNA lesion, 8-oxo-20-deoxyguanosine (8-oxo-dG) in both liver and lungs of mice. When the mice was treated with curcumin and curcumin plus piperine prior to the administration of single dose of BaP, there was marked decrease in the levels of 8-oxo-dG content and %DNA in the comet tail in both lung and liver tissues. The anticancer effect exerted by curcumin is due to its antioxidant properties that inhibit free radicals from mediating peroxidation of membrane lipids or oxidative DNA damage since both induce the development of cancer. In order to determine the level of DNA damage, %DNA was investigated in the comet tail as it is linearly related to DNA break frequency over wide range of damage. It is expected that the supplementation of curcumin and curcumin plus piperine shows a significant decrease in the %DNA damage in the comet tail in BaP administered groups [35].