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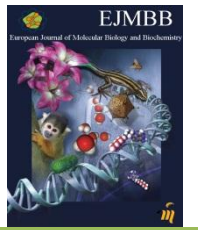

BIO-ENHANCER: A PHARMACOGNOSTIC PERSPECTIVE

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ABSTRACT
Bio-enhancers are themselves not therapeutic entities but when combined with an active drug lead to the potentiation of the pharmacologic effect of the drug. Bio-enhancers can be classified based on their natural origin and various mechanisms elicited by them when in combination with drugs to improve their bioavailability. Such formulations have been found to increase the bioavailability / bioefficacy of a number of drugs even when reduced doses of drugs are present in such formulations. The need for bio-enhancers arises due to drugs which are poorly available, administered for long periods, toxic and expensive. The various bio-enhancers available are pepper, garlic, caraway, Cumin and lysergol, naringin, quercetin, niaziridin, glycyrrhizin, stevia, cow urine distillate ginger. Out of these, *Cuminum cyminum* and niaziridin are the potential bio-enhancers of future. This article reviews the improvement of drug bioavailabilities exhibited specially by natural compounds from plants mentioned above.

INTRODUCTION

Plant based medicines are used by a majority of the world's population. Our Ayurveda texts have a mention of thousands of herbal drugs for various diseases including the rare ones [1]. Plant based medicines is used by about 60% of the world population and most of the third world countries still depend on herbal medicines. Almost 25% of modern pharmacopoeias too contain drugs of plant origin [2]. Bioavailability is the rate and extent to which a substance enters systemic circulation and becomes available at the required site of action [3]. Maximum bioavailability is attained by drugs administered via intravenous route, whereas drugs administered orally are poorly bioavailable as they readily undergo first pass metabolism and incomplete absorption. Such unutilized drug in the body may lead to adverse effects and also drug resistance. Thus, there is need of molecules which themselves have no same therapeutic activity but when combined with other drugs / molecules enhance their bioavailability. Many synthetic and herbal drugs suffer from the problem of low bioavailability [4]. Many natural compounds from medicinal plants have capacity to augment the bioavailability when co-administered with another drug. Thus bio-enhancers are chemical entities which promote and augment the bioavailability of the drugs which are mixed with them and do not exhibit synergistic effect with the drug [5].

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Novel properties of Bio- enhancers

- Nontoxic to humans or animals,
- Should be effective at a very low concentration in a combination,
- Should be easy to formulate and
- Most importantly, enhance uptake/absorption and activity of the drug [6]

There are various advantages of using bio-enhancer in combination therapy are as follows –

- Efficacy of drug is increase due to increase in bioavailability.
- Combination of bio-enhancer with drug reduces the dosage and dangers of drug resistance can be minimized.

- Adverse drug reaction/side effect and toxicity of drug will be minimized because of reduced dosage. This is especially true of anticancer drugs like Taxol.
- There are ecological benefits too eg. Toxol used to treat ovarian cancer or breast cancer is derived from bark of Pacific yew tree, one of the slowest growing trees in the world. At present to treat one patient, six trees, 25-100 years old need to be felled with bio-enhancers fewer trees will be destroyed.
- They can reduce inter-individual variability as well as intra-individual variability as they increase the bioavailability of drug [7].

Table 1. Classification of Bio-enhancers Based on Origin

Plant Origin		Animal Origin
Niaziridin	Capsaicin	Cow urine distillate (Kamdharu ark)
Cuminumcyminum	Quercetin	
Carumcarvi	Curcumin	
Stevia	Naringin	
Ginger	Capmul	
Aloe vera	Peppermint oil	
Ammannaimultiflora	Gallic acid	
	Ellagic acid	
	Ferulic acid	
	Lysergol	
	Glycyrrhizin	
	Allicin	
	Simomenine	
	Genistein	
	5'-Methoxy hydnocarpin	

Table 2. Classification of Bio-enhancers Based on Mechanism of Action [8]

Inhibitors of P-gp efflux pumps are other efflux pumps	**Example:** Carumcarvi(caraway), Genistein, Sinomenine ,Cuminum cyminum (Black cumine), Naringin, Quercetin.
Suppressors of CYP-450 enzyme and its isozymes	**Example:** Naringin, gallic acid and its ester, quercetin
Regulators of GIT function to facilitate better absorption.	**Example:** Aloevera (Aloe), Niaziridin (Drumstick pods), Zingiber officinal (ginger), glycyrrhizin (Liquorice)

Table 3. Physico-chemical Properties of Piperine [9-12]

S.No	IUPAC	1-[5-(1,3-Benzodioxol-5yl)-1-oxo-2,4pentadienyl]piperidine
1	Chemical name	1- piperoylpiperidine
2	Molecular formula	C17H19NO3
3	Molecular mass	285.34 gm mol^{-1}
4	Percentage composition	C= 71.55%, H=6.71%, N=4.91% and O=16.82%
5	Taste	Tasteless at first, but burning aftertaste
6	Melting point:	130°c
7	Density	1.193 gm cm^{-3}
8	pK (18°)	12.22
9	Solubility	Insoluble in water, soluble in benzene and acetic acid
10	Stereoisomer	isopiperine, isochavicine and chavicine
11	UV absorption maxima (methanol)	332 nm

Figure 1. Chemical structure of Piperine

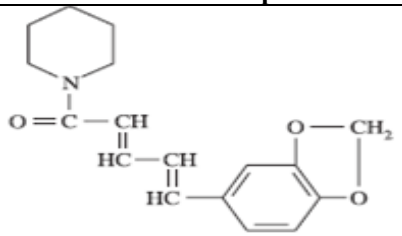


Figure 2. Chemical structure of Quercetin

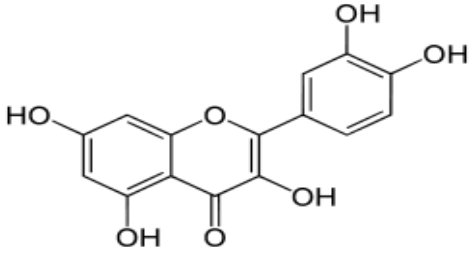
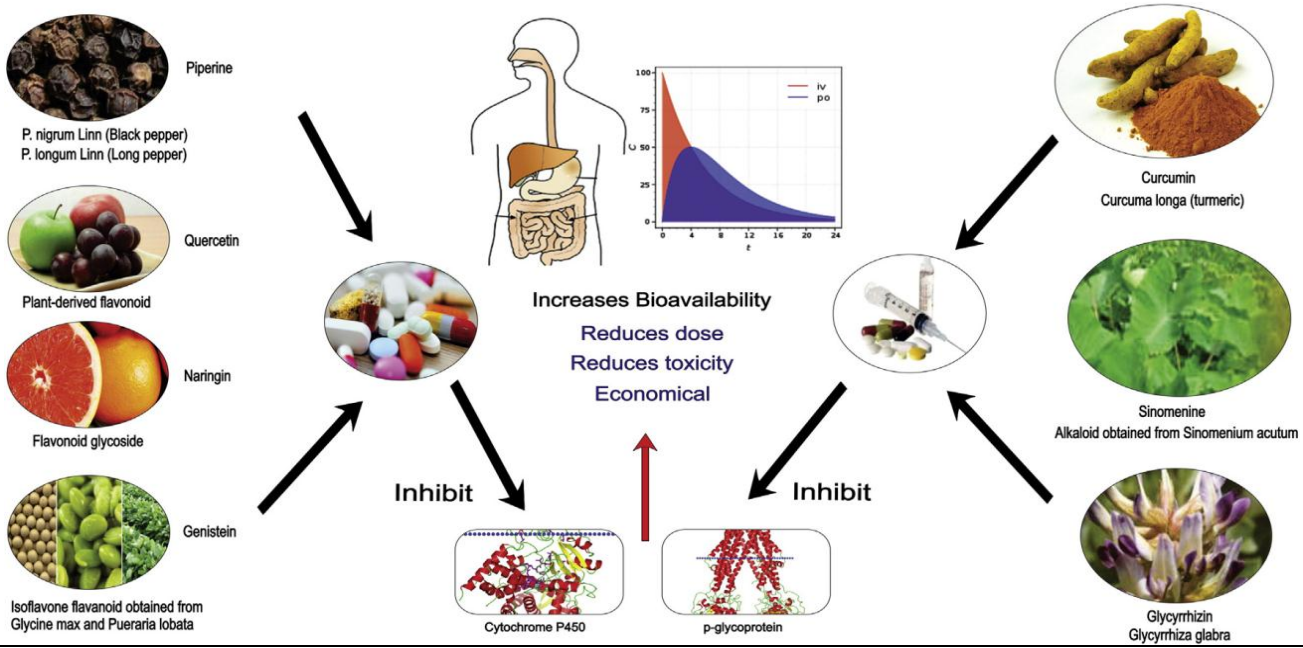


Figure 3. Bioavailability Enhancement Mechanism



1) Bio-enhancers of herbal origin

Herbal medicine is a practice as old as mankind and during the last century chemical and pharmacological studies have been performed on a lot of plant extracts in order to know their chemical composition and to confirm the indications of traditional medicine [13]. Ayurveda has made a major contribution to the drug discovery process through reverse pharmacology, with new means of identifying active compound and reduction of drug development cost [14].

The concept of 'bioavailability enhancers' is derived from the traditional age old system of Ayurveda (science of life). In Ayurveda, black pepper, long pepper and ginger are collectively known as "Trikatu". In sanskrit "Trikatu" means three acrids. The action of bio-enhancers was first documented by Bose (1929) who described the action of long pepper to *Adhatoda vasika* leaves increased the antiasthamatic properties of *Adhatoda vasika* leaves [15]. Phytochemical and phytopharmacological studies have long been established overall health boosting capacities of various plant products but there is a great interest and medical need for the improvement of bioavailability of a large number of herbal drug and plant extract which are poorly lipid soluble and so are less bioavailable[16].

Most of the plant constituents, specifically phenolics, are water soluble and so the major problem for less bioavailability is the inability to cross the lipid membranes of intestine. The bioavailability can be improved with the use of different novel delivery systems like liposomes, marinosomes, niosomes and lipid based systems which can enhance the rate of release as well as the capacity to cross the lipid rich biomembranes [17]. Phospholipids based drug delivery systems have been found to be promising for the effective and efficacious herbal drug delivery. The effectiveness of any herbal product (or medication) is dependent upon delivering an effective level of the active compounds [18].

2) Role of Bio-enhancers

There is a growing interest in improving the bioavailability of a large number of potent drugs by combining it with natural bio-enhancers [19-21]. A bio-enhancer 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 [22].

Several drugs due to their low lipophilicity or Zwitterion character at physiological pH [22] or because of poor hydrophilicity or efflux by P-glycoprotein [23] are unable to cross the biological membranes. Therefore, the use of natural bio-enhancers has gained importance in the current scenario to improve the pharmacokinetic parameters and hence bioavailability of various potent drugs [24,25].

The various mechanisms by which natural bio-enhancers 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,[26]

c) Modifications in the permeability of the GIT epithelial cell membrane [27,28]

d) Cholagogous effect,

e) Bioenergetics and thermo genic properties and [29]

f) Suppression of first pass metabolism and inhibiting drug metabolizing enzymes and stimulation of the activity of

gamma glutamyltranspeptidase (GGT) enzyme which enhances the uptake of amino acids[30,31] .

They help in reducing the dose of drug, shorten the duration of treatment, lower the drug resistance problems, minimize drug toxicity and adverse actions 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[32].

3) Bio-enhancing activity of Piperine

Members of the botanical family piperaceae were among the first cultivated plant and the species of the genus Piper are the important medicinal plants used in various systems of medicine [33]. Piperine was discovered by Hans Christian Ørsted in 1819. It is known as one of the main components of pepper [34]. Piperine is responsible for the pungency of black pepper and long pepper, along with chavicine (an isomer of piperine)[35]. Piperine is a nitrogenous pungent substance [36].

The chemical structure of piperine places it in the group of cinnamamides[37].The congeners of cinnamamides possess sedative, hypnotic, anticonvulsant, antidepressant, and skeletal muscle relaxing properties[38]. Highly pure piperine is needle-shaped or short rod-shaped light yellow or white crystalline powder. It yields salts only with strong acids. The solution of piperine in alcohol has a pepper-like taste [38].

Piperine is rapidly absorbed through the GIT and could be detected in plasma as early as 15 min after administration to rat [39]. 97% of piperine was absorbed after oral administration of piperine at a dose of 170 mg/kg to the male albino rats. 3% of the administered dose was excreted up to 4 days as piperine in the feces and it is not detectable in urine. Piperine did not go undergo any metabolic change during absorption from intestine but latter it is metabolized rapidly by liver and other tissue and maximum plasma concentration was attained at about 6 hr. Urine is the major excretion route for piperine metabolites in rats as no metabolite could be detected in faces[40].

4) Bio-enhancing activity of Quercetin

(2-(3,4-dihydroxy phenyl)-3,5,7-trihydroxy-4Hchromen-4-one) is a flavonoid, an aglycone form of a number of other flavonoid glycosides found in citrus fruits[41]. Quercetin has exhibited a wide range of beneficial biological activities including antioxidant, radical scavenging, anti-inflammatory, anti-atherosclerotic, anti-tumoral and anti-viral effects [41]. Quercetin has been shown to increase bioavailability, blood levels and efficacy of a number of drugs including diltiazem [42], digoxin[43-44] and epigallocatechingallate [45]. The plasma concentrations, the area under the plasma concentration-time curve (AUC) and peak concentration C(max)] of diltiazem in the rabbits pretreated with quercetin were significantly higher than those obtained from untreated group[46,47].

5) Bio-enhancing activity of Ginger oleo-resin

The drug consist of oleo-resin isolated from the rhizome of the plant *Zingiber officinalis* Roscoe, family Zingiberaceae, commonly known as ginger. Many drugs are found to be more active when used in combination with bio enhancer products developed from oleo-resin of ginger. The effective range for ginger oleo-resin as a bio-enhancer is 10-150 mg.The major pungent compounds in *Zingiber officinale*(Ginger) of rhizome extract contain potentially active gingerols, which can be converted to shogaols, zingerone, and paradol. Gingerols increase the motility of the gastrointestinal tract and have analgesic, sedative, antipyretic, and antibacterial properties gingerol is the major pungent principle of ginger. The chemopreventive potentials of gingerol present a promising future alternative to expensive and toxic therapeutic agents [48,49].

Ginger acts powerfully on GIT mucous membrane. The role of ginger is to regulate intestinal function to facilitate absorption. The composition containing *Z. officinale* alone provides bioavailability/bio-enhancing activity in the range of 30–75%. Piperine and *Z. officinale* provides the bioavailability of drugs in the range of 10–85%.The dosage of bio-enhancer from *Z.officinale* as the range of 10–30 mg/kg body weight. The dosage of bio-enhancer from *Z.officinale* as bioactive fraction is in the range of 5–15 mg/kg body weight, preferably 30 mg/kg body weight and piperine is in the range of 6–10 mg/kg body weight, preferably 8 mg/kg body weight. The extracts or its fractions either in presence or absence of piperine have been found to be highly selective in their bioavailability enhancing activity. It varies from almost nearly significant (20%) to highly significant (200%) [50,51].

CONCLUSION

The researchers are now aimed at methods of increasing the bioavailability of various plant extract which has been available to a wider section of the society. Hence, it has been proved that novel drug delivery system of herbal has been used to increase the bioavailability of the compounds or their respective constituents. Concept of bio-enhancer is based on traditional system of Indian medicines. Bioavailability enhancing effect of natural compounds could be attributed to inhibition of P-gp and oxidative metabolism with minimal toxic effects. Therefore, co-administration of natural compounds is expected to be one of the promising approaches to enhance the absorption and bioavailability of drugs. The advent of the natural bio-enhancers tends to exert a positive influence on the economy of a country by reducing the dose of the drug as well as drug development cost. It minimizes the toxicity resulted from the over dosage of the poorly bioavailable drug. It also shortens the duration of treatment and minimizes the drug resistance problems. Being natural it is also safe, easily available, non-addictive, and free from side effects and adverse effects.

Therefore, several natural compounds can be utilized in enhancing the absorption and bioavailability of various potent drugs.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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