

Bioenhancers from Mother Nature: A Paradigm for Modern MedicinesDr. Surender Verma^{1*}, Suchita Rai²¹Assistant Professor, Department of Pharmaceutical Sciences, KUK, Kurukshetra, Haryana, India²Research Scholar, Department of Pharmaceutical Sciences, KUK, Kurukshetra, Haryana, India**Review Article*****Corresponding author**

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Abstract: Pharmaceutical corporations round the globe have continually been within the urge of discovering innovative blockbuster medicine for numerous ailments by outlay billions of bucks for the drug discovery programmes. With the development of various 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 (CYP) DMEs within the gut wall and within the liver is the major process which is responsible for reduced bioavailability of drug. Additionally to the present, EDTs like P glycoprotein (P gp), multidrug resistant associated protein (MRP) are also liable for reduced bioavailability of the therapeutically active medication, particularly metastatic tumor medication. Therefore, a certain alternative is needed which can enhance the bioavailability of these drug molecules. Bioenhancers plays a vital role in modifying the pharmacokinetic and pharmacodynamic profile of these drugs. A bioenhancer is an agent which when co-administered with the drug, enhances its bioavailability. Herbal bioenhancers play an important role in enhancing the bioavailability and efficacy of various categories of medicine, like antihypertensives, anticancer, antiviral, antitubercular and antifungal medication at low doses. This paper demonstrates numerous natural agents including quercetin, genistein, naringin, sinomenine, curcumin, and glycyrrhizin as potent bio enhancer's drugs and additionally describes planned mechanism of action that in the main includes absorption method, drug metabolism, and action on drug target. The bioenhancers are simply accessible, safe, and free from side effects, minimizes drug toxicity, shortens the period of treatment, lowers the drug resistance issues and minimizes the value of treatment. This review also presents a detail study about various aspects of bio enhancer and a short account of the various natural products showing enhancing effect.

Keywords: Bio enhancers, Bioavailability, Natural bio enhancers.

INTRODUCTION

Bioavailability is the term coined to rate and extent with which any substances reach the systemic circulation and shows the desired action [1]. There are various classes of drugs which have potent therapeutic activity, but due to their poor bioavailability, their use has always been a crucial aspect of drug development programmes. Factors responsible for poor bioavailability of drugs are the physicochemical properties of the drug and biological barriers. Factors such as poor aqueous solubility, poor intestinal membrane permeability, first pass metabolism and poor stability of the drug in the gastrointestinal tract (GIT), comes under physicochemical barriers whereas, the biological barrier comprises hepatic and intestinal drug metabolizing enzymes and efflux drug transporters. The metabolism of drugs by drug metabolizing enzymes (DMEs) in the gut wall and the liver is the major contributors of reduced bioavailability of drugs. In addition to this, P-glycoprotein (P-up) is also responsible for reduced bioavailability of the

therapeutically active drugs, especially anticancer drug. The drug administered through oral route undergoes various steps such as incomplete drug absorption and first-pass metabolism which ultimately leads to low bioavailability. Enhanced bioavailability leads to increase in the level of drug in the blood stream and thus increase efficacy and reduce the drug dosage. Till date myriad of methods such as micronization, disaggregation of micronized molecules, specific or time-release preparations, solubilisation of active drug and polymorphic/crystal form selection and nanotechnology has been appointed for enhancing the bioavailability [1, 2]. Many compounds from plant origin have the potential to augment the bioavailability of the main drug. Thus, Bio enhancers are the compound which does not possess any typical pharmaceutical activity but when co-administered with the main moiety enhance the activity of the drug in several ways. Moreover, efficacy is enhanced by increased bioavailability. The term bioenhancer was first time analysed by Bose in 1929 who observed that

there was increase in the antiasthmatic property of vasaka (*Adhatoda vasica*) leaves when it was given in combination along with long pepper. The ideal or concept of 'bioavailability enhancers' from plant origin can be tracked back from our Ayurveda system of medicine. "Trikatu", which is a Sanskrit word meaning three acrid, was very famous during the period between the 7th century B.C. and the 6th century A.D. It was one of the ancient ayurvedic preparations used for the treatment of various types of ailments. Trikatu was a combination of long pepper (*Piper longum* Linn.), black pepper (*Piper nigrum* Linn.), and ginger (*Zingiber Officinale* Rosc.), which contains active component piperine, which has the potential to enhance the bioavailability of various drugs, nutrients etc. Several factors related to a drug such as low lipophilicity or zwitter ionic character at physiological Ph, poor aqueous solubility or presence of P-glycoprotein on the outer surface makes the drug unable to cross the biological membranes. Therefore, the use of natural bioenhancers such as Genistein, Sinomenine, Curcumin, piperine has gained importance in the current scenario to improve the pharmacokinetic and pharmacodynamics

profile of the drug and hence bioavailability of various potent drugs [3].

Ideal properties of bio- enhancers [4]

The bio-enhancer used should possess various novel properties such as:

- It should be Nontoxic to humans or animals,
- It should show its effect at a very low concentration in a combination.
- Should be easy to formulate and
- The Most important property which every bioenhancer should possess is that it should enhance uptake/absorption and activity of the drug.

CLASSIFICATION OF BIOENHANCERS [5]

There is two scale based on which bio enhancers can be classified. They can be classified as either:

- a) By their origin.
 - Plant origin.
 - Animal origin.
- b) By the mechanism of action through which the act.

Table-1: Classification of Bioenhancers based on plant origin.

Bio-enhancer	Biological Source
Piperine(black pepper)	<i>Piper longum (long pepper) and Piper nigrum (black pepper)</i>
Gingerol(Ginger)	<i>Zingiberofficinale</i>
Glycyrrhizin (Liquorice)	<i>Glycyrrhizaglabra</i>
Caraway(cumin)	Carumcarvi
Black cumin	Cuminumcyminum
Quercetin	Citrus fruits
Niaziridin	Drumstick pods
Capsaicin	Capsicum annum
Stevia	Honey leaf
Allicin(garlic)	Allium sativum
Curcumin(Turmeric)	Curcuma longa

Table-2: Classification of Bioenhancers based on animal origin

Cow urine distillate: (Kamdhenu ark)

Table-3: Classification of Bioenhancers based on the mechanism of action

Inhibitors of P-glycoprotein (P-GP) efflux pump and other pumps: EXAMPLES: Cuminumcyminum (black cumin), Carvumcarvi (Caraway), Genistein, Sinomenine, Naringin, Quercetin.
Inhibitors of CYP-450 enzyme and its isoenzymes EXAMPLES: Sinomenine, Naringin, Quercetin. Quercetin, Naringin, Gallic acid
Regulators of GIT function to facilitate better absorption: EXAMPLES: Niaziridin (drumstick pods), Glycyrrhizin (liquorice), Aloe vera (Aloe), Zingiberofficinale (ginger).

Bioavailability enhancement mechanism of different natural bioenhancer [6-8]

There are several mechanisms of action through which natural bioenhancers show their action of improving bioavailability. Different herbal enhancers may have common or different mechanisms of action.

Bioenhancers mainly increase the bioavailability of nutraceuticals by acting on the gastrointestinal tract which enhances drug absorption whereas there are various antimicrobial bioenhancers which act by altering the metabolic process of the drug.

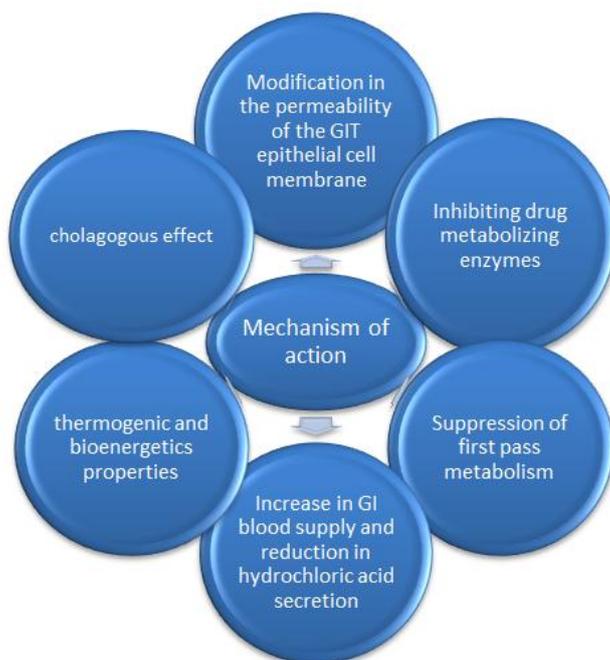


Fig-1: Mechanism of different natural bioenhancer

In addition to the above-mentioned mechanisms, few other postulated theories for herbal bioenhancers are:

- Inhibition of gastric emptying time, gastrointestinal transit and intestinal motility.
Stimulation of gamma-glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids
- Increasing the blood circulation which leads to absorption of an orally administered drug.

- Bioenhancers also act by inhibiting P-glycoprotein which is an efflux pump and moves out the drug thus prevents the drug from reaching the targeted site. Thus in such case bioenhancer inhibit the action of P-glycoprotein.

The bioavailability enhancement mechanism of various agents possessing the capability of enhancing the bioavailability of API is shown through fig.1.

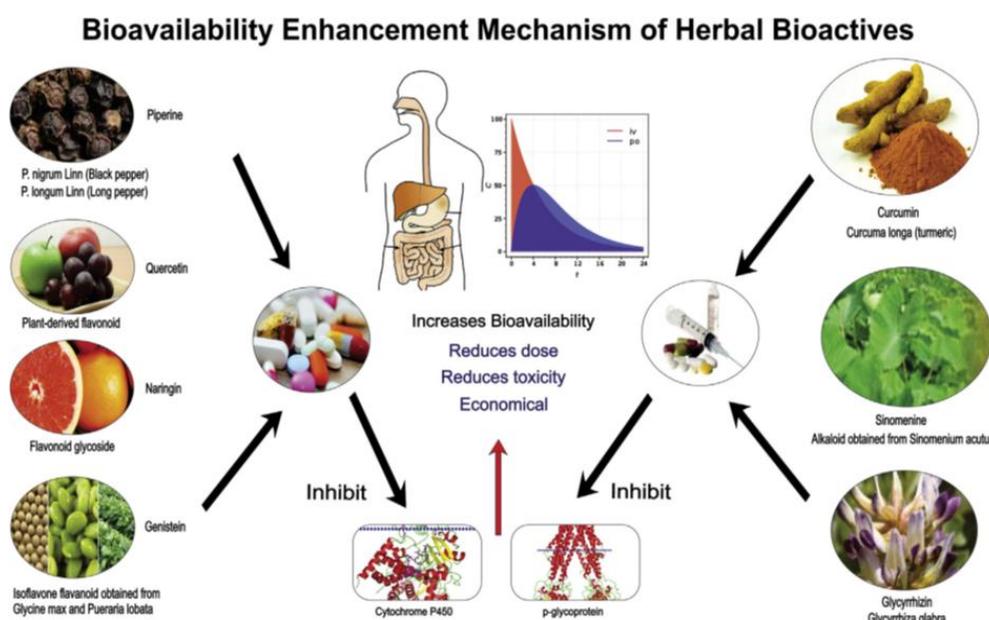


Fig-2: bioavailability enhancement mechanism of herbal bioactives

Role of natural compounds from medicinal plants as drug bioavailability enhancers [9-15]

In this section various natural bioenhancers which has the bioavailability enhancement ability when through co-administration with the main drugs are introduced:

Naringin

Naringin which is categorised as flavonoid glycoside is the main constituent of grape fruit. Naringin is responsible for the bitter taste of grapefruit.

Naringin has various pharmacological actions such as antioxidant effect, blood lipid lowering ability and anti-carcinogenic function. Naringin was reported to shows its bio-enhancing property by inhibiting-gp and CYP3A1/2 in rats. Oranaringin, in the dose of 3.3 and 10 mg/kg, when given 30 min before intravenous administration of paclitaxel (3 mg/kg) and after intravenous administration of paclitaxel, the AUC was significantly improved. It was found to be 40.8% when naringin was administered in the dose of 3.3and 49.1% for naringin dose of 10 mg/kg.

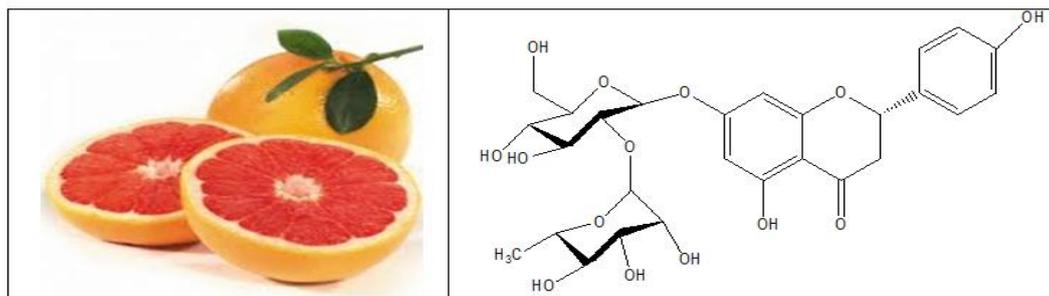


Fig-3

Ginger (*Z. officinale*)

Due to the presence of saponin, flavonoids and alkaloids ginger has the potential to act on GIT mucous membrane. Ginger shows its action by regulating intestinal function which enhances the rate of absorption. When used in the range of 10-30 mg/kg body weight it acts as bioenhancer. Ginger shows its

action on various antibacterial, antiviral and anti-carcinogenic drugs. It exhibited significant increasing bioavailability of different antibiotics like Azithromycin (85%), Erythromycin (105%), Cephalexin (85%), Cefadroxil (65%), Amoxycillin(90%) and Cloxacillin (90%).

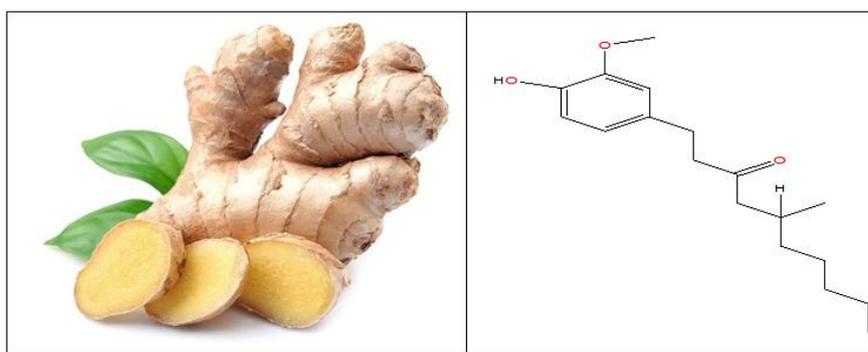


Fig-4

Garlic (*Allium sativum*)

Allicin, which is regarded as active bioenhancer moiety present in garlic upraise the antifungal activity of the drug. Amphotericin B when co-administered along with *Allium sativum* was founded more effective against pathogenic fungi such as *Candida albicans* and *Aspergillus fumigatus* in addition to yeast *Saccharomyces cerevisiae*.

Curcumin

Principal curcuminoid obtained from *Curcuma longa* (turmeric). Curcumin is found in every Indian

family and is frequently used as spices. Curcumin is used as bioenhancer for antimicrobial agents and anticancer drug. Curcumin shows its activity by suppressing drug metabolizing enzymes (CYP3A4) in the liver as well as inducing changes in the drug transporter P-glycoprotein which leads to increase in Cmax and AUC of any drugs. Increase in anticancer activity of docetaxel by curcumin in rats was reported by Yan et al. Curcumin in the quantity of 100 mg/kg was administered in a group of rats 30 min before the administration of docetaxel.

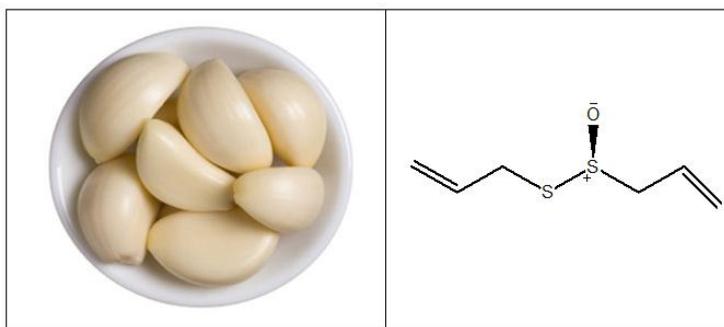


Fig-5

The rats treated with curcumin prior to the administration of docetaxel showed an enhanced AUC from 282.6 ± 18.4 (control) to 2244.1 ± 68.0 ng h/ml, an approximately eight-fold increase in the AUC, and in the C_{max} from 102.5 ± 11.5 (control) to 1024.2 ± 121.7 ng/ml, an approximate tenfold increase in C_{max} as

compared to the control group. It was reported that Curcumin itself possess anticancer activity in the body. Thus we can use curcumin with the combination of an anticancer drug like docetaxel to enhance the anticancer activity of the drug.

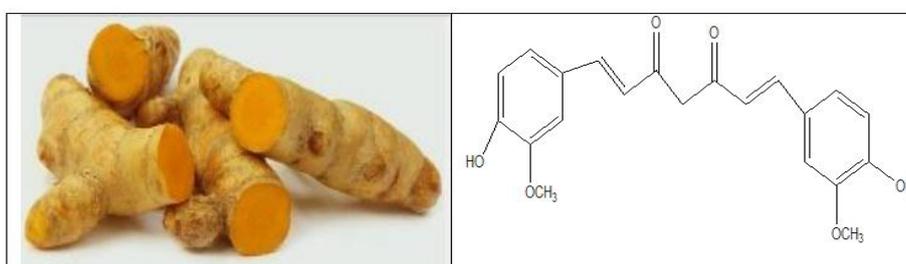


Fig-6

Piperine

Piperine is a potent plant alkaloid obtained from *P. nigrum* Linn (Black pepper) and *P. longum* Linn (Long pepper). Piperine has a various pharmacological effect such as anti-inflammatory activity, antipyretic activity, antifungal activity, antidiarrheal activity, antioxidant, antithyroid, antidepressant activity, analgesic activity etc. Piperine

is scientifically regarded as world's first bioavailability enhancer. Piperine shows its action by promoting rapid absorption of drugs and nutrients, and also by inhibiting enzymes which leads to biotransformation of drugs. It is a potent inhibitor of P-gp efflux transporter present in gastrointestinal wall. Piperine was found to increase the bioavailability of rifampicin by about 60% and hence reduce the dose from 450 to 200mgRifampin.



Fig-7

Cumin/Caraway (*Carum carvi*)

Cumin seeds have various pharmacological actions such as carminative, mild stomachic and diuretic actions. The major active constituents of the seeds are carvone and limonene. The effective dose for the *Carum carvi* to act as bioenhancer is in the range of 1-55 mg/kg body weight. It has been reported to enhance bioavailability of antibiotics, antifungal, antiviral, anticancerous and Anti-TB drugs like

Rifampicin, Pyrazinamide and Isoniazid. It is also found to be more effective as bioenhancers when used in combination with bioenhancer from *Zingiber officinale* (10-150 mg/kg body weight) and piperine (3-15 mg/kg body weight). The bioenhancing property of *Carum carvi* is due to either enhancing the mucosal or serosal permeation which leads to effective absorption of drugs or due to its effect on the P-gp transporter.

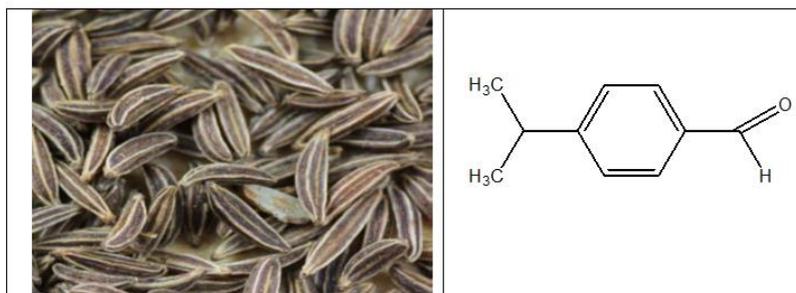


Fig-8

Indian Aloe (*Aloe vera*)

Aloe vera is obtained from dried juice of the leaves of *Aloe barbadensis* Mill. Effect Aloe vera on the absorption of vitamin C and E was studied, and from the result, it was observed that aloes improve the

absorption of both the vitamin C and E. The absorption is slower and vitamins last longer in the plasma with aloes and increase the bioavailability of Vitamin C and E in human. Aloe vera may be a promising future nutritional, herbal bioenhancer.

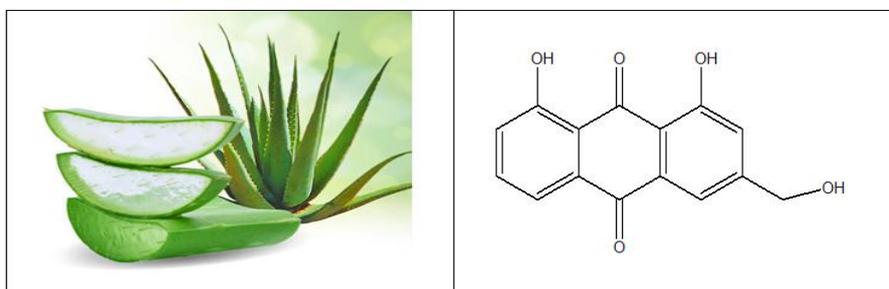


Fig-9

Liquorice (*Glycyrrhiza glabra*)

Liquorice consists of dried, peeled or unpeeled, root and stolon of *Glycyrrhiza glabra*. Glycyrrhizin is the active constituent found in Liquorice

which enhances the bioavailability of rifampicin by 6.5 fold at the concentration of 1 µg/ml. It also enhances the bioavailability of anticancer drug taxol by fivefold at the concentration of 1 µg/ml.

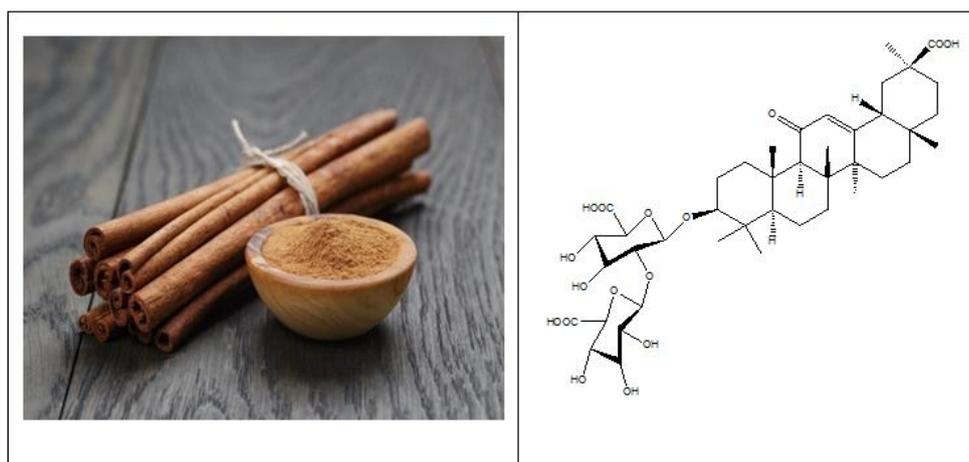


Fig-10

Cow's Urine Distillate

Cow urine distillate is regarded as an effective bioenhancer. It enhances the transportation of various antibiotics like rifampicin, tetracycline and ampicillin across the gut wall by 2-7 folds. Cow urine also lead to enhancement in the potency of taxol against MCF-7 cell lines. Bioavailability of rifampicin get enhanced by 80

fold when cow urine is used in the concentration 0.05 µg/ml, ampicillin by 11.6 fold in 0.05 µg/ml concentration and clotrimazole by fivefold in 0.88 µg/ml concentration. The bioenhancing property of cow urine is by facilitating absorption of drugs across the cell membrane.



Fig-11

Capsaicin

It is an active component of *Capsicum annum* and other chilli species. Capsaicin leads to enhancement

of various drugs. It enhances the bioavailability of theophylline.

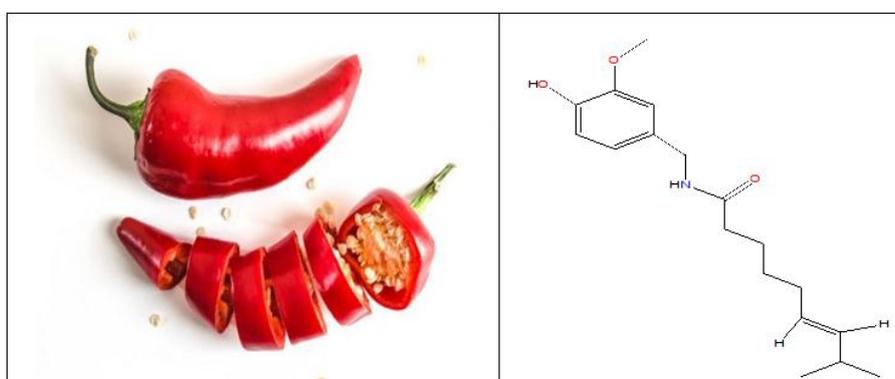


Fig-12

Table-4: List of Herbal Formulations

S.no	Formulation	Active moiety	Pharmacological activity	Application	Ref
1	Quercetin Liposome	Quercetin	Anti-oxidant Anti-cancer	Reduced dose, enhanced penetration in blood	16
2	Curcumin Liposome	Curcumin	Anti-cancer	Long circulation with high entrapment efficiency	17
3	Garlicin Liposome	Garlicin	Lungs disorder	Increase efficiency	18
4	Liposome encapsulated Silymarin	Silymarin	Hepatoprotective	Improve bioavailability	19
5	Naringenin loaded nanoparticles	Naringenin	Increases antioxidant activity and increases bioavailability	Antioxidant and anticancer	20
6	Quercetin microspheres	Quercetin	Anti-cancer	Significantly decreases the dose size	21

Table-5: List of various herbs, its source, mechanism and their dose as a potent bioenhancer

S.No	Compound	Source	Action	Dose	Drugs
1	Naringin	It is a flavanoid glycoside found naturally in citrus fruits, especially in grapefruit	Act by inhibiting the CYP3A1/2 enzymes and p-glycoprotein.	3.3 and 10 mg/kg	Paclitaxel, Verapamil, Diltiazem
2	Ginger	Rhizome of the perennial plant <i>Zingiber officinale</i> Roscoe	Regulate intestinal function and facilitate absorption	10-30 mg/kg	Antibiotics like Azithromycin, Erythromycin, Cephalexin, Cefadroxil, Amoxycillin and Cloxacillin
3	Garlic (Allicin)	Aromatic bulb of <i>Allium sativum</i> Linn.		120µM	Fungicidal activity of Amphotericin B
4	Curcumin	Dried and fresh rhizomes of <i>Curcuma longa</i> Linn.	Curcumin suppresses drug metabolizing enzymes (CYP3A4)	12g/day	Celiprolol and Midazolam
5	Piperine	Seeds of <i>Piper longum</i> Linn. and <i>Piper nigrum</i> Linn.		15 mg/kg.	Rifampicin (Antituberculous), Nimesulide, Diclofenac sodium (NSAIDS), Beta lactams(Antibiotics), Theophylline (Antiasthmatic)
6	Cumin/Caraway	Dried ripe seeds of <i>Carum carvi</i> Linn.,	Enhancing the mucosal or serosal permeation which leads to effective absorption of drugs	1-55mg/kg	Antibiotics, antifungal, antiviral and anticancerous drugs. Therapeutic activity of Anti-TB drugs like Rifampicin, Pyrazinamide and Isoniazid
7	Indian aloe (Leaves)	Dried juice of the leaves of <i>Aloe barbadensis</i> Mill.,	In combination with vitamins, leads to slower absorption and last longer in the plasma and increases bioavailability of Vitamin C and E	-	Vitamin C and E
8	Liquorice (Glycyrrhiza glabra)	Dried root and stolon of <i>Glycyrrhiza glabra</i>	enhances cell division inhibitory activity	1 µg/ml	Taxol and antibiotics like Tetracycline, Nalidixic acid,

		Linn., Family			Ampicillin etc
9	Cow's Urine Distillate	-	Facilitate absorption of drugs across the cell membrane	0.05 µg/ml and 88 µg/ml	Antibiotics like rifampicin, tetracycline and ampicillin and anticancerous drug taxol.
10	Capsaicin	Fruit of <i>Fraxinus annuum</i> Linn., Family- Solanaceae	Increase the absorption of the drugs. AUC of the drugs.	- -	Theophylline

Marketed formulation [10, 22]

Risorine: Risorine is a rifampicin containing fixed dose combination product, approved in India for the use as an antitubercular drug in place of rifampicin 450 mg and isoniazid 300 mg.

Composition: Each capsule of resorine contains

Rifampicin 200 mg IP, Isoniazid 300 mg IP, Piperine 10 mg

Dosage: For adult, one resorine capsule to be taken once daily, one hour before or two hours after meals with a full glass of water.

Indication: It is used for treatment of all forms of tuberculosis in which organisms are susceptible to rifampicin and isoniazid

Table-6: Showing patent on herbal formulation [23]

US patent No.	Active ingredients	Novel system
US 5948414 (Jack G. Wiersma) (Sep. 7, 1999)	Opioid analgesic and aloe	Nasal spray
US6890561 B1 (Yoav Blatt) (May 10, 2005)	Isoflavones	Microencapsulated formulation
US6896898 B1 (Weihong Xiong) (May 24, 2005)	Alkaloids of aconitum species	Transdermal delivery system
US patent 2005/0142232 A	Oleaginous oil of Sesamum indicum and alcoholic extract of Centella asiatica	Brain tonic
US patent 2007/0042062 A1	Extract of curcumin, Zingiber officinalis	Herbal tablet dosage form
US patent 2007/007284A1	Opioid analgesic	Transdermal patch
US patent 7569236132	Flavonoids (such as quercetin) and terpenes	Microgranules

HURDLES [24]

Bioenhancers has made a great revolution in the field of drug delivery, but still, there are various hurdles which are still needed to be surmounted to meet with all the success. The newly developed Bioenhancers have many challenges to be faced. One of the challenges related with bioenhancer is an improvement in the properties of drug formulations like circulation in blood, increased functional surface area, protection of encapsulated drug from degradation, crossing biological barriers & site-specific targeting. Large-scale production of bioenhancer is another problem associated with the use of bio enhancer. Pilot scale production of bioenhancer is easy than large-scale production. Advances in herbal bio-enhancers also provide new challenges for regulatory control. There is an increasing need to have regulations that would account for drug products.

Future perspectives [25]

The concept of bioenhancer which has started from the use of "trikatu" from Ayurveda has successfully taken the lead to various modern medicines to enhance their bioavailability. The Ayurvedic concept of hupaan and sehpaan ought to be incorporated into the modern medicine also. The researchers are now aimed at using bioenhancer along with the main pharmacological drug as a method of reduction of drug dosage, and thus drug treatment cost making treatment available for financially challenged peoples. Various researches related with the development of bioenhancers of herbal and non-herbal origin are in process.

CONCLUSION [26]

The innovative concept of Bioenhancers which was the result of a traditional system of medicines made a great revolution in the field of medicines. Use of bioenhancer along with the main drug has led to a reduction in drug cost, increased bioavailability and has

minimised drug dosage. Various research works have been done for developing Piperine derivatives and other novel bioenhancers. Natural bioenhancers are safe, free from a various side effect, effective, economical, easily procured, and has a widely-based effect on several classes of drug. Bioenhancers also lower the drug resistance and thus reduce the cost of therapy. A synthetic process for its commercial production has been developed for industrial use.

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