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Exploring the Potential of Herbal Bioenhancers: A Comprehensive Review

Shruti Wadaskar*

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ABSTRACT:
Herbal bioenhancer is an agent of herbal origin or any phytomocule,which is capable of enhancing bioavailability and bioefficacy of particular drug or nutrient with which it is combined ,without any typical pharmacological activity of its own at dose used.The term bioavailability enhancer was fisrt coined by Indian Scientist at the Regional Research Laboratory,Jammu(now know as Indian Institute of Integrativ Medicine)discovered and scientifically validated piperine as the world's first bioavailability enhancer in 1979.The concept of bioenhancer of herbal origin can be tracked back from the ancient knowledge of Ayurvedic system of medicine. The use of bioenhancers is the method used for increasing bioavailability of an orally administered drug. This approach leads to improved formulation with enhanced oral bioavailability of the active ingredient.Bioenhancer can be classified based on their plant as well as on animal origin to improve the bioavailabilty of drugs.They reduce the dose, shorten the treatment period and thus minimize drug - resistance problems. Due to dose - economy, they make treatment cost affordable, reduce drug toxicity and adverse drug reactions. The various bioenhancers available are piperine, garlic, carum carvi, cuminumcyminum, lysergol, naringin, quercetin, niaziridin, glycyrrhizin, stevia, cow urine distillate ginger.Out of these, Cuminum cyminum and niaziridin are the potential bioenhancers of future. Therefore,the need of the hour is to carry out extensive research on these bioenhancers so that they could be utilised in the drug formulations. They have also shown to improve oral absorption of nutraceuticals like vitamins, minerals, amino acids andcertain herbal compounds.

Keywords: Bioefficacy,Bioavailability,Herbal Bioenhancer,Drugs,Piperine.

I. INTRODUCTION:

A bioenhancer is an agent which is capable of intensifying the bio - availability and bioefficacy of a drug with which it is co-administered without any pharmacological activity of its own at therapeutic dose used.[1]Herbal bioenhancer or herbal biopotentor is an agent of herbal origin or any phytomolecule ,which is capable of enhancing bioavailability and bioefficacy of particular drug or nutrient with which it is combined without any typical pharmacologicgal activity of its own at the dose used.It is natural agent that is capable of enhancing drug bioavailabilty upon its co- administration with the active pharmaceutical ingredient . This conception is kindly new to ultramodern drug.Numerous studies have shown medicine bioavailability enhancement when different bioenhancer sources were co-administered. This has led to some promising approaches, such as advances in prodrugs, micronizations,delayed-release drugs, sustained-release capsules, absorption enhancers and permeability enhancer dosage forms. [2]

Herbal medicine is practice as old as human existenceand during the last century chemical and pharmacological studies have been performed on lot of plant extract in order to know their chemical composition and to confirm the indications of traditional medicines.[3]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 costs.[4]Recent development of another Ayurveda based technology,this time enhancing bioavailability of drugs have produced a revolutionary shift in the way medicine are administred.Phytochemical and phytopharmacological studies have long been established overall health boosting capacities of various plant product but there is great interest and medical need for improvement of bioavailability of large of number of herbal drug and plant extract which are poorly lipid soluble and less bioavailable.[5]

There is a great interest and medical need for the enhancement of bioavailability of a large number of drugs which are inadequately bioavailable, given for long periods, and are poisonous and expensive. Poor bioavailable medicine remain sub-therapeutic because a major portion of a dose never reaches the plasma or exerts

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its pharmacological effect unless and until very large doses are given which may lead to serious side effects. Any significant enhancement in bioavailability will affect in lowering the dose or the dose frequency of that particular drug . Incomplete oral bioavailability has various causes. These include poor-dissolution or low aqueous solubility, poor intestinal membrane saturation, degradation of the drug in gastric or intestinal fluids and presystemic intestinal or hepatic metabolism. [6]

Herbal bioenhancers are Phytomolecules that, in controlled doses, enhance the biological activity of therapeutics or their bioavailability. Their development is grounded on ancient knowledge of Ayurveda. The herbal bioenhancers are easily available, safe and relatively free from side effects, minimizes drug toxicity, shortens the duration of treatment, lowers the drug resistance problems and minimizes the cost of treatment. An effective bioenhancer is nontoxic to both humans and creature, easy to concoct, and largly responsive, even when its concentration in a given enhancer/drug combination is low. Useof bioenhancersis found essential with the drugs which are poisonous, expensive, and inadequately absorbable and administered for long period of time. Therefore, bioenhancers can be used in combination therapy with drugs such as antihypertensives, antimicrobials, anticancer, antiviral, antitubercular and antifungal drugs and nutrients such as vitamins, minerals, herbal extracts and amino acids. Hence for the treatment of infectious diseases combination therapy can be applied in human and veterinary medicine.

About 250 million doses of antibiotics are consumed annually and 20-50 % of its use is unnecessary or irrational. Indiscriminate use of antibiotics promotes multiple drug resistanceand infected individuals have to consume more amount of antibiotics may be due to reduced absorption in gut, restrictive uptake by target microbe and operation of efflux pump. Antibiotics along with feed additives have been used in the livestock and poultry industry in a large scale since long time. Emergence and spread of Anti-Microbial Resistance (AMR) and Multiple Drug Resistant (MDR) infections and antibiotic associated health ailments as a sequel of antibiotic therapy made researcher focus on alternative medicine. Among alternates, the traditional herbal medicines making possible to identify novel bioactive compounds hasattracted the attention of researcher's world over. [7]

Definition:

Bioenhancers are compound that,when combined with pharmacological substances stimulate and enhance drug bioavailabilty without having a synergistic activity with drug.Bioavailability enhancers are chemicals that, on their own, don't have the same effect as a traditional medicament.But when combined, they enhance drug macromolecular activity in a number of ways, including boosting drug bioavailability all across membranes, enhancing the drug molecule using conformational interactions, serving as drugs molecule receptors, and enhancing drug sensitivity in target cells. "A 'bioenhancer' is a chemical that increases the bioavailability and effectiveness of a medication it is combined with without having its own pharmacologicalaction at the dose used.[8] There are various benefits of using natural bioenhancer and are given in Fig.1[9]

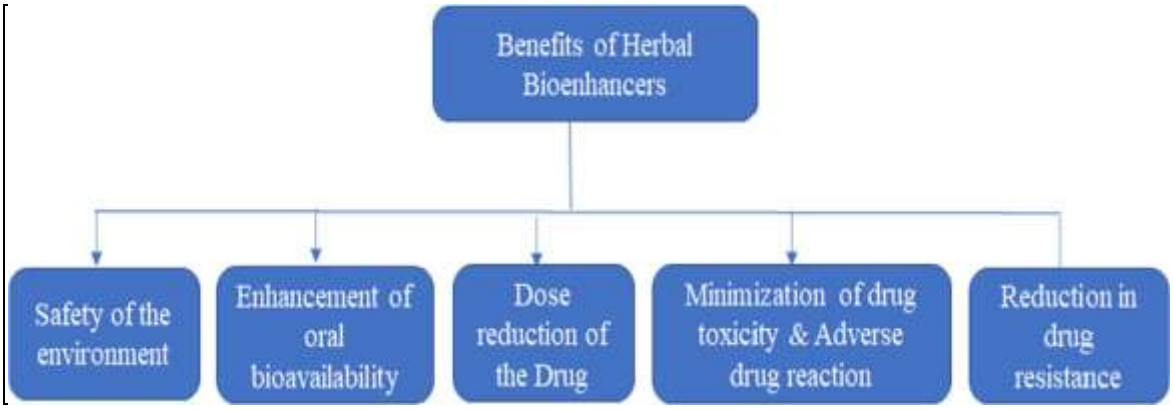

Fig. 1:Benefits of Herbal Bioenhancers

International Journal of Pharmaceutical Research and Applications
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History of Bioenhancer:

The term bioavailability enhancer or bioenhancer was first coined by Indian scientists C.K. Atal, the Director of the Regional Research laboratory, Jammu, who discovered and scientifically validated Piperine as the world's first bioavailability enhancerin 1979. Bioenhancers are molecules, which do not possess drug activity of their own at the dose used but promote and augment the biological activity or bioavailability or the uptake of drugs in combination therapy.[1] C.K. Atal, the Director of the institute scrutinized a list of ancient Indian Ayurvedic formulations used in the treatment of a wide range of diseases. He found that one of the groups of herbals which has been documented very frequently as essential part of about 70% of Ayurvedic prescriptions, is `Trikatu`, that comprises three acrids viz. long pepper, black pepper and dry ginger in equal proportions. He observed that a majority of Ayurvedic formulations contained either Trikatu or else one of the ingredients of Trikatu, namely Piper longum used in a large variety of diseases. In subsequent experiments using various drugs and extracts with trikatu and its ingredients they found that mainly piperine enhances the bioavailability of most of the drugs used in experiments and the role of ginger is to regulate intestinal function to facilitate absorption. [10,11,12]Apart from Piperine, which has the honour to be first bioenhancer, many other natural active constituents also possessed bioenhancement capability. Every bioenhancers have specific properties. Some may have similarities and differences in increaseing the bioavailability of different drugs by using different mechanism of action. [13]

Need of Bioenhancer:

.Bio-enhancers are such agents, which by of drugs even when reduced doses of drugsthemselves are not therapeutic entities but when combined with an active constituent proceed to the potentiating of the pharmacological effect of the drug. Such formulations have been found to increase bioavailability or bio-efficacy of a numberof drugs even when reduced doses of drug are present in such formulation. Many synthetic and herbal drug suffer from the problem of low bioavailability. Bioavailability is the extent and rate towhich a substance enters total systematiccirculation and becomes available at the required site of action.[14]

These are phyto-molecules development ofwhich is based on ancient knowledge ofAyurveda. They enhance the bioavailabilityof drugs when administered at low doses. Due to this dose is decreased, reduces duration of treatment thus drug-resistance problem also reduce.The treatment is made cheaper,reduce drug toxicity and reduce in adverse reaction. When used in combination with number of drug classessuch as antibiotics, antituberculosis, antiviral, antifungal and anticancer drugs they are quite effective.[15]

Ideal Properties of Bioenhancer:

- It should be non toxic in nature.
- It should be simple to formulate.
- It should enhance the absorption and activity of the drug.
- It must be non irritating and allergy free.
- It should be stable and quick to react.
- Compliance is simple. [16,17]
- It should be effective at very low concentration in combination.
- Should enhance activity of drug molecule.
- Enhance uptake and absorption. [18]

Advantages:

- When a bioenhancer is used in combination with a medicine, the drug's dosage is decreased, and the possibility of drug resistance is minimised.
- Adverse drug reaction or side effects, as well as drug toxicity, will be decreased as a result of thelower dose.
- This is particularly true with anticancer medications such as Taxol.
- Due to an improvement in bioavailability, the drug's efficacy has increased.
- As drug bioavailability is increased, they can lower both inter-individual and intra-individual variability.[9]
- Reducing the dose can decrease the cost factor also,make the treatment economical.

Disadvantages:

- Researching and developing bioenhancer for largescale manufacturing is a challenge.
- Laboratory or pilot technologies must always be scaled up for ultimate commercialisation. Scaling-up problems include low nanoparticle concentrations, aggregation, and the chemical process; it is easier to modify nanoparticles in the laboratory.
- Regulations regulating the physiochemical and pharmacokinetic features of newer bioenhancers are required. [19]

International Journal of Pharmaceutical Research and Applications
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Classification of Bioenhancers:
The bio enhancers are classified into two different classes on the different basis. There are two classes of bio enhancers which are as follows:

1] Bio enhancers based on origin (Table-1)
2] Bio enhancers based on mechanism of action (Table-2)

Table 1:Based on origin

SrNo.	Origin	Examples
1.	Plant Origin	Piperine,Glycyrrhizin,Cumin,Ginger,Stevia, Niaziridin,Allicin,Caraway,Curcumin,Aloevera,Guggul,Lysergol,Turmeric,Capsaicin, Quercetin,Genistein,Sinomenine,Capmul, Peppermint oil,Turmeric,Gallic acid.
2.	Animal Origin	Cow urine distillate (kamdhenu ark).

Table 2:Based on mechanism of action[8]

Sr No.	Mechanism of action	Examples
1.	Inhibitors of P-glycoprotein efflux pump and other pumps:	Cuminumcyminum (black cumin), Carvum carvi (Caraway), Genistein, Sinomenine, Naringin, Quercetin.
2.	Inhibitors of CYP-450 enzyme and its isoenzymes:	Quercetin, Naringin, Gallic acid and its esters.
3.	Regulators of GIT function to facilitate better absorption:	Niaziridin (drumstick pods), Glycyrrhizin (liquorice), Aloe vera (Aloe), Zingiber officinale (ginger).

A detailed description of some of the bioenhancers based on the above classification system is as follows:

1.Piperine: Piperine (1-piperoyl piperidine) is an amide alkaloid found in plants of Piperaceae family like Piper longum (long pepper), Piper nigrum (blackpepper). The bioenhancing property of piperine wasfirst utilized in the treatment of tuberculosis in human. Piperine was found to increase the bioavailability of rifampicin by about 60% and hence reduce the dose from 450 to 200 mg. In human medicine piperine is approved to be combined with antitubercular drugs. Piperine also showed enhanced bioavailability when combined with Nevirapine, a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase which is used in combination with other antiretroviral agents for the treatment of HIV-1 infectio. [20]

2.Turmeric: Turmeric (Curcuma longa) is a common household item used as remedy for various ailments. Curcumin, a flavonoid from turmeric suppresses drug metabolizing enzymes like CYP3A4 in liver and is also capable of inducing change in drug transporter P-gp and thus increased the bioavailability of celiprolol and midazolam in rats .[21] The bioenhancer nature of curcumin is similar to piperine .[22] Curcumin suppresses UDP-glucuronyl transferase level in intestine and hepatic tissues.[23]

3.Allicin: It is an allyl sulphur compound obtained from garlic (Alliumsativum).Allicin enhances the fungicidal activity of Amphotericin B against pathogenic fungi such as Candida albicans,

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Aspergillus fumigatus and yeast Saccharomyces cerevisiae. Amphotericin B when given along with Allicin exhibited enhanced antifungal activity against S. cerevisiae.[8]

4.Naringin: Naringin is the major flavonoid glycoside found in grapefruit, apples, onions and tea. It exhibits pharmacological actions like anti-oxidant, anti-ulcer, anti-allergic and blood lipid lowering. Naringin is capable of inhibiting intestinal CYP3A4, CYP3A1, CYP3A2, P-gp and thus acts as a bioenhancer. Pretreatment with oral ingestion of naringin 3.3 and 10mg/kg improves the AUC for intravenous paclitaxel (3 mg/kg) in a dose dependent manner. [24]

5.Quercetin: Quercetin is a flavonoid; an aglycone form of a number of other flavonoid glycosides found in citrus fruits. It exhibits anti-oxidant, radical scavenging, anti-inflammatory, anti-atherosclerotic activities. Quercetin has been shown to increase bioavailability, blood level and efficacy of a number of drugs including diltiazem, digoxin, verapamil, etoposide, and paclitaxel.[13,24]

6.Genistein: Genistein is a phytoestrogen belongs to the isoflavone class of flavonoids found in a number of dietary plants like soyabean (Glycine max) and kudzu (Pueraria lobata). It is a P-gp and BCRP efflux pump inhibitor. The presence of genistein (10 mg/kg) causes an increase in AUC by 54.7% and a decrease in total plasma clearance by 35.2% after oral administration of paclitaxel at dose of 30 mg/kg.[13,24]

7.Caraway: Caraway/cumin which is a P-gp efflux pump inhibitor consists ofthe dried ripe fruits of Carum carvi of family Umbelliferae. Itshows anti-oxidant, anti-microbial, diuretic and carminative. The main constituents are carvone and limonene. The effective dose of the bioenhancer extract is in the range of 5-100 mg/kg body weight.Percentage enhancement of bioavailability for rifampicin is 110%,for cycloserine is 75%, for ethionamide is 68%.Apart from the above bioenhancing effects, caraway also enhancesthe bioavailability of anti-biotics.[25]

8. Niaziridin(Drumstick Pods): It contains niaziridin, a nitrile glycoside which is a powerful bioenhancer. It regulates GIT functions to facilitate betterabsorption. It enhances the bioavailability of rifampicin by 38.8 folds at 1.0 ug/ml. It also enhances the bioavailability of Clotrimazole by 5-6 folds.An in-vitro study of active fraction of M. oleifera pods against Mycobacterium tuberculosis (H37Ra) exhibited no antituberculosis activity at the concentration at which it enhanced theanti-tubercular activity of rifampicin[26]

9.Liquorice: Liquorice consists of dried, peeled or unpeeled, root and stolon of Glycyrrhiza glabra and exhibits anti-hepatotoxic, anti-fertility,anti-inflammatory, expectorant and anti-oxidant activity. It contains glycyrrhizin which enhances the bioavailability of rifampicin by 6.5 fold at the concentration of 1 ug/ml. It also enhances the bioavailability of taxol by 5 fold at the concentration of 1 ug/ml.[27]

10.Ginger: It contains Gingerol which facilitates better absorption by regulating GI tract function.The effective dose of the bioenhancer extract is in the range of 10-30 mg/kg body weight.It enhances the bioavailability of rifampicin by 65% and ethionamide by 56%. It also enhances the bioavailability of antibiotics (Azithromycin – 78%), anti-fungal (Ketoconazole 125%), anti-viral (Zidovudine – 105%) and anti-cancer (5-fluorouracil – 110%) drugs.[28]

11.Stevia(Honey leaf): Stevia is anti-hypertensive agent and also promotes insulinsecretion. The bioenhancing chemical constituent present in Stevia is stevioside.Though the mechanism of action is not known, it enhances the bioavailability of anti-tubercular, anti-leprotic, anti-cancer, antifungal and anti-viral drugs.The effective dose of the bioenhancer extract is in the range of0.01-50 mg/kg body weight.[29]

12.Peppermint oil: Peppermint oil significantly improves the oral bioavailability of cyclosporine. Co-administration of 100 mg/kg peppermint oil almost tripled the Cmax and AUC of cyclosporine. It exerts its mechanism of action probably by CYP3A inhibition.[30]

13.Sinomenium acutum: Sinomenine is an alkaloid extracted fromSinomenium acutum .[31]It is found to increase the bioavailability of paeoniflorin by inhibition of P-gp efflux pumps. Paeoniflorin is used in the treatment of inflammation and arthritic conditions but has a poor absorption rate and thus a very low bioavailability (3 – 4%) when administered orally.[32]

14.Gallic acid: Gallic acid exerts a synergistic effect when administered with piperine and provides a more pronounced therapeutic potential in reducing beryllium-induced hepatorenal dysfunction and oxidative stress consequences. [33]Gallic acid esters like propyl gallate, octyl gallate, aluryl gallate etc. have been found to enhance bioavailability of several drugs like nifedipine [34].

15. Cow urine distillate (Kamdhenu ark) : Cow urine distillate is more effective as a bioenhancer

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 1203-1211 www.ijprajournal.com ISSN: 2249-7781

than cowurine. It enhances the transport of antibiotics like rifampicin,tetracycline and ampicillin across the gut wall by 2-7 folds [35]. It also enhances the potency of taxol against MCF-7 cell lines [36]. It enhances the bioavailability of rifampicin by 80 fold in 0.05 ug/ml concentration, ampicillin by 11.6 fold in 0.05 ug/ml concentration and clotrimazole by 5 fold in 0.88 ug/ml concentration. Cow urine also has antitoxic activity against the cadmium chloride toxicity and it can be used as a bioenhancer of zinc [2].

Mechanism of Action Of Bioenhancer:

There are different chief mechanisms via which the various bio-enhancers exert their properties of increasing bioavailability on the drug molecule.

1.By enhancing the absorption of orally administered drugs from GIT.

2. By means of modulating the active transporters located in various locations.

E.g. P-glycoprotein (P-gp) is pumps out drugs because it is efflux pump and avoid it from reaching the target site.

3. Decreasing the elimination process thereby extending the sojourn of drug in the body.

4. Inhibiting the drug metabolizing enzyme like CYP3A4, CYP1A1, CYP1B2,CYP2E1, in the liver,gut,lungs and various other locations. This will facilitate to overcome the first pass effect administered drug.

5. Inhibiting the renal clearance by preventing glomerular filtration, active tubular secretion by inhibition P-gp and facilitating passive tubular re absorption .[37,38]

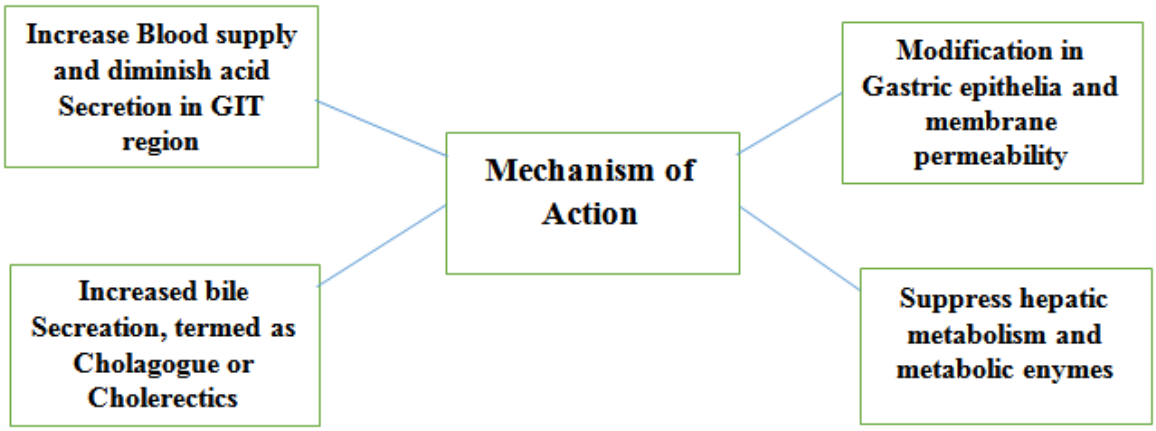

Fig.2:Common Mechanism of Natural Bioenhancers[8]

Method of Bioenhancement of Bioenhancer:

1. Absorption enhancers:

Many of the absorption enhancers are constructive in enhancing the intestinal absorption, such as bile salts, surfactants, fatty acids, chelating agents, salicylates and polymers. Chitosan, particularly trimethylated chitosan, improves the drug absorption via the paracellular route by redistribution of the cytoskeletal F - actin, causing the opening of the tight junctions. Bile, bile salts and fatty acids are surfactants which act as absorption enhancers by elevating the solubility of hydrophobic drugs in the aqueous layer or by increasing the fluidity of the apical and basolateral membranes. Calcium chelators like ethylene glycol tetra acetic acid and ethylene diamine tetra acetic acid (EDTA) increase the absorption by decreasing the extracellular calcium concentration, leading to the disruption of cell-cell contacts [38].

2. Prodrugs:

Various ampicillin derivatives are the well-known examples of increasing the lipophilicity of agents, to enhance absorption of a polar drug by the strategy of prodrug. Ampicillin because of its hydrophilic nature is only 30% - 40% absorbed from the gastrointestinal tract. By esterification of carboxyl group of ampicillin, the produgs of ampicillin such as pivampicillin, bacampicilln and talampicillin were synthesized [8].

3. Dosage form and other pharmaceutical approaches:

Many dosage formulations such as liposomes and emulsions enhanced the intestinal absorption of insoluble drug. Particle size reduction methods such as micronization, nanoparticular carriers, complexation and liquid crystalline phases also maximize drug absorption [13].

International Journal of Pharmaceutical Research and Applications
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4. P-glycoprotein inhibitors:

P-glycoprotein inhibitors reverse P – glycoprotein - mediated efflux in an attempt to improve the efficiency of drug transport across the epithelial membrane. P - glycoprotein inhibitors influence the metabolism, absorption, distribution, and elimination of P-glycoprotein substrates in the process of modulating pharmacokinetic[39].

Hurdles With Bioenhancers:

Although bio-enhancers in drug delivery have been successful, not all approaches have met with the same success.New bio-enhancers being developed come with challenges which have to be surmounted. One of the challenges is to improve on properties of drug formulations such as long circulation in the blood, increased functional surface area, protection of incorporated drug from degradation, crossing of biological barriers and site specific targeting.challenge of research and development of herbal bioenhancers is large scale production. There is always a need to scale up laboratory or pilot technologies for eventual commercialization. The challenges of scaling up include low concentration of nanomaterials, agglomeration and the chemistry process; it is easier to modify nanomaterials at laboratory scale for improved performance than at large scale.Advances in herbal bio-enhancers also provide new challenges for regulatory control. There is an increasing need to have regulations that would account for physicochemical and pharmacokinetic properties of nano drug products, which are different from conventional drug products.[8]

Regulatory Approved Formulation With Bioenhancers:

Drug Control General of India (DCGI) has approved the marketing of antitubercular formulation named Risorine in the Indian market, containing 200 mg of rifampicin, 300 mg of isoniazid (INH) and 10 mg of Piperine by Cadila Pharma in November 2009.Piperine increased bioavailability of rifampicin by about 60%. Therefore,adding the bioenhance‘Piperine’reduced the dose of rifampicin from 450to 200 mg. Thus, reducing the dosage, cost and toxicity of rifampicin[2].

II. CONCLUSION:

The cost of therapy in poor countries like India is amajor challenge for modern medicine. Systematic and imaginative techniques are needed to reduce these costs. Researchers are currently investigating strategies to reduce drug doses, and thus treatment costs, so thattherapy becomes relatively accessible to a wide range of patients, including the poor. technology is based on the existing medical system, but it is a rapidly evolving sector.New methods of drug discovery are advancing rapidlybut the economics of drug development are a concern.Researchers are currently working on a way to reduce drug doses, and thus the cost of treatment, and make therapy accessible to broad populations, including financial support for the country. The bioenhancingphenomenon is useful in a variety of situations and provides relief to society because of its side effects.

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