

Biopotentiality using Herbs: Novel Technique for Poor Bioavailable Drugs

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Abstract: Herbal source has been used by mankind recently at very high rate due to their lower risk benefit ratio in compared to the modern allopathic medicines. Concept of biopotentiality was not so novel it has been so far used in old times by ayurvedic peoples so called as Yogvahi. Bibliographic investigation revealed about such agents which cause potentiation of the pharmacologic effect even if administered at lower dose with active ingredient. Piperine, naringin, quercetin, glycyrrhizin, genistein, sinomenine, nitrile glycoside and cow urine distillate have capability to augment and enhance the bioavailability. A bioenhancer do not introduce its own therapeutic action with the actual active principle at the therapeutic dose used. Augmentation of bioefficacy reduces dose, toxicity and adverse effects so in return shorten the time and cost of treatment. These concept covers drug categories like antibiotics, antitubercular and anticancer and cardiovascular which are so potent in nature and require quite immediate effects. Aim of this review paper is to acknowledge the scientific society about various available natural bioavailability enhancers with their brief mechanism of action and pharmacotherapeutics application when supplemented with therapeutic ingredients. Future practices and studies are indeed for improvement in drug bioavailability exhibited particularly by natural compounds and find out some more novel agents from the wide array of unexploited herbs that have capability of biopotentiality or bioenhancing. Integration of aged and time trusted Ayurveda with modernized allopath always brings a new breakthrough in medicines.

Keywords: Herbal, Biopotentiality, Yogvahi, Piperine, Bioenhancers, Bioavailability.

INTRODUCTION

Use of natural medicines either from animal or herbal is a well known scientific practice that's aged equals to mankind. Nature originated medicines are the first choice of the most of the peoples worldwide that makes them so popular around the globe. Official books and compendia contain modern drugs but almost one fourth of them are of natural sources. Ayurveda has a significant and worthy contribution in new drug discovery as well as in reduction of drug development costs [1, 2]. Research has come with number of new molecules these days but suffering from disease of low oral bioavailability [3]. Low membrane permeability is the major cause of this hat may be due to lower lipophilicity, ionic characteristics, poor water solubility or P-glycoprotein [4, 5]. Aim of enhancing and improving oral bioavailability, a number of approaches have emerged out like use of prodrugs, absorption enhancers and permeability enhancing novel drug delivery systems like emulsions and liposome [4]. Use of P-glycoprotein's inhibitors in the aim of achieving good bioavailability is the major area of interest.

Ayurveda had come with concept of reverse pharmacology in old time and now another Ayurveda-based technology of enhancing bioavailability of drugs is a remarkable milestone in field of medicines [2, 5]. The concept of bioenhancers or biopotentiators is called “Yogvahi” that meant to use herbs to increase or potentiates plasma concentration of drug. Piperine of black pepper was the first in this series as the major part of “Yogvahi”. [6]The review reminds the knowledgeable scientific society that modern pharmaceutical researchers are targeting mainly economics of treatment and finding the strategies how to lower cost of the novel drug development or a delivery system. Reduction in cost makes them easy to provide the finest treatment of medicine at an affordable price all the sections of society. To alleviate bioavailability is best way to reduce dose, toxicity and cost of drug dosage form, so use of herbal biopotentiators or bioenhancers with the core drug is the best way to achieve this target. Uses of such agents are applicable not only for humans but also for animals in normal practices whether it is medicine or nutrition. However it was also found that piperine not always increases the bioavailability in some cases the effect was found null [7].

Origin of concept

At most first case comes in light as an evidence of biopotentiality was reported in Pharmacographia Indica,” by the scientist named Bose in 19th century. This is about the alleviation of antiasthmatic activity *vasacin* due to co administration of piperin [8]. In 1979 Indian Scientists (Indian Institute of Integrative Medicine, Jammu) discovered and confirmed Piperine (Black pepper) as the world’s first bioavailability enhancer and coined the term. But since 7th century B.C. and the 6th century A.D ancient ayurvedic scientist were using “Trikatu” Churn as carrier for many other herbs or herbal nutrients because Trikatu contains piperin and piperin is a bioenhancers [9]. However, this phenomenon of co-supplementation of the core therapeutic agent with a secondary agent gained popularity since the traditional times up to this 21st century worldwide. This area has covered major categories of molecules lacking a good bioavailability like respiratory, CVS, CNS, GIT, antitubercular, antibiotics and antineoplastics [10].

Drug absorption barriers

The drug must cross many anatomical and biological barriers to achieve its pharmacological action and therapeutic effectiveness. There are many layers like structures in epithelium of intestine which act like a barrier between transportation of drug molecules from GIT to systemic circulation. List of barriers which stick around the transportations are hydrophilic aqueous stagnant layer, lipid bilayers at cell surroundings, aqueous channels for small molecules and trans membrane P glycoprotein (Pgp) efflux pumps[11, 12] as given below (Fig 1). A drug molecule has to travel a path of lumen to internal cave of but through wall and at last via hepatic metabolism to systemic circulation.

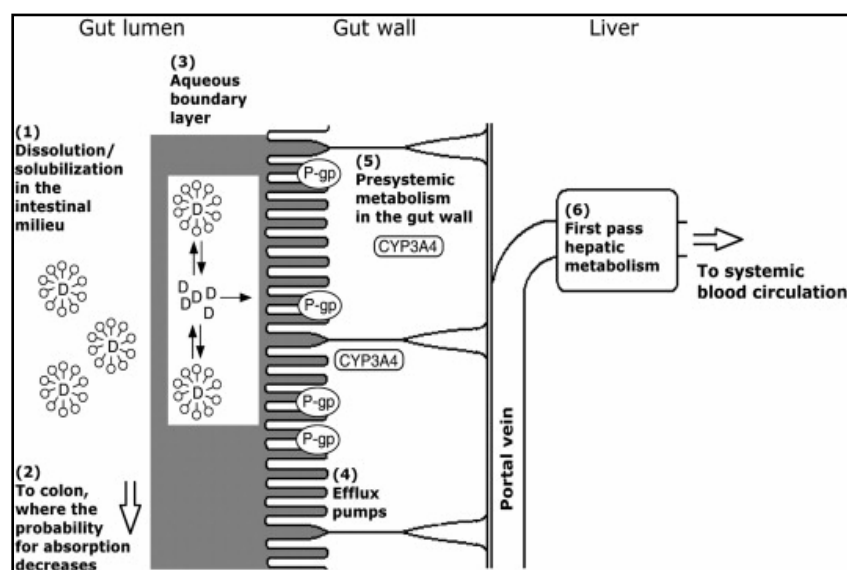
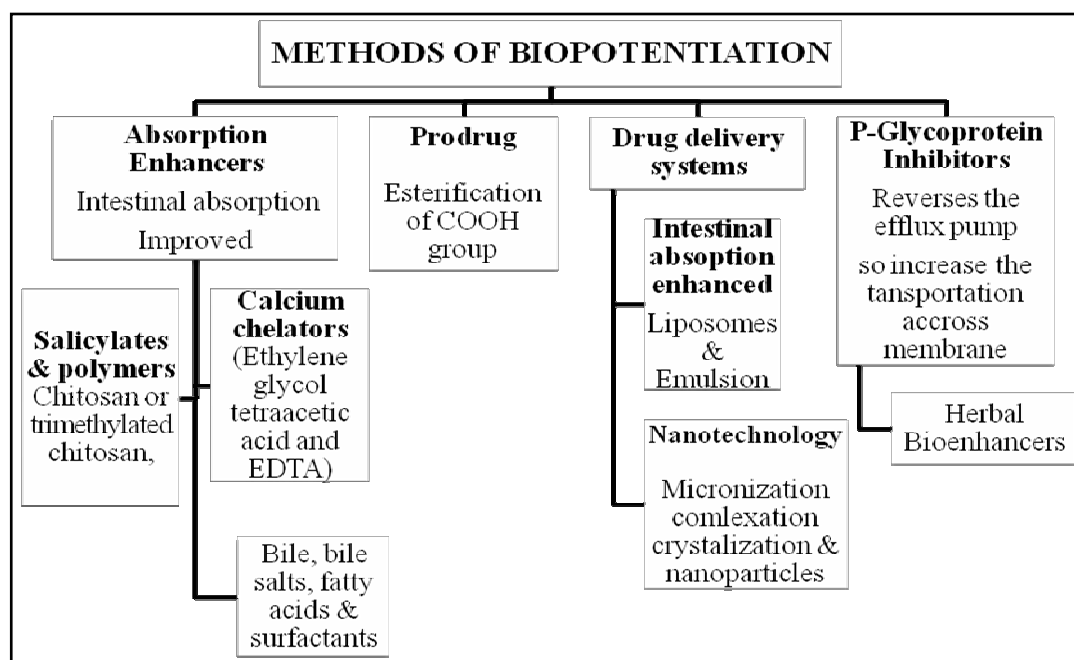


Figure: 1 Drug absorption barriers

METHODS OF POTENTIATION OF PHARMACOLOGICAL ACTIVITY**Figure2:- Different methods of biopotentialion****RATIONALE OF BIOPOTENTIATION OR BIOAVAILABILITY ENHANCING**

“The phenomenon of increasing the total availability of any chemical entity (nutrient or drug molecule) in biological fluid or systemic circulation is called biopotentialion or bioenhancement and the secondary agents which are responsible for this augmentation of plasma concentration of principle ingredient are termed as Biopotentialioners or Bioavailability enhancers”.

Criteria of selection active ingredients

- Drugs adhered with poor bioavailability need higher dose to overcome the subtherapeutic range and exert its pharmacological effect because a large portion of dose gets consumed before it reached to target.
- For those drugs which have to be administer for a long period of time like in cancer or cardiovascular disease
- Drugs having number of toxic effects and adhered to higher risk benefit ratio need to use this concept. Some time, to attain the MEC or MIC a high dose is used that also increase the fatal side effects on the other side. This has been seen in case of antineoplastics, antiviral, and multidrug resistance.
- Expensive drug molecules need to use cautiously because of very high cost of each milligram of drug.

Advantage of bioenhancement

Bioavailability is directly proportional to the available plasma concentration so ultimately related therapeutic efficacy.

1. This can make the expensive drugs affordable by lowering the dose or dosing frequency. Shortening the treatment period also increase the acceptance of patients mainly in case of chemotherapy. It comforts the patient in terms of cost also.
2. Reduce the required dose ultimately reduce the toxic effects.
3. Therapeutic treatments which include heavy doses, accompanied by loss of metals and vitamins available in body. The bioenhancers improve the nutritional status of body while duration of course [9, 13].

MECHANISMS OF ACTION OF HERBAL BIOENHANCERS

Mechanisms of action differ as per type of herbal bioenhancers selected for the purpose. Nutritional type bioenhancers act on gastrointestinal tract (GIT) and enhance absorption whereas antimicrobial type of bioenhancers acts on metabolism pathway. Commonly followed mechanisms of action by most of biopotentials are depicted below in chart [Fig 3]. Herbal bioenhancers used as an agent to potentiate the pharmacological effect of the core ingredient. Piperine and other herbal bioenhancers can be segregated as per their mechanism of action [14]. Piperine was the first herbal biopotential or bioenhancer introduced by ayurveda in form of Trikatu churna. Piperine has following proposed mechanism of action.

- **Inhibition of drug metabolism pathways:** It acts on drug metabolizing enzymes responsible for drug metabolism and degradation when go through liver. It inhibits mainly P-glycoprotein class and CYP3A4 (Cytochrome P-450). Some of other enzymes of Cytochrome P-450 class inhibited or induced include CYP1A1, CYP1B1, CYP1B2, CYP2E1 and CYP3A4. P-glycoprotein is the major efflux pump of cell, mainly important in case of antimalarial or antineoplastics. This pump throws out the ingested drug. [15]
- **Inhibition of Glucouronic acid:** It interferes with the extent of glucuronidation in gut. Mainly it lowers the endogenous UDP-glucuronic acid content and also by inhibiting the transferase activity. In several experimental studies on rats piperine has demonstrated strong inhibition of UDP-glucuronyl-transferase [16].

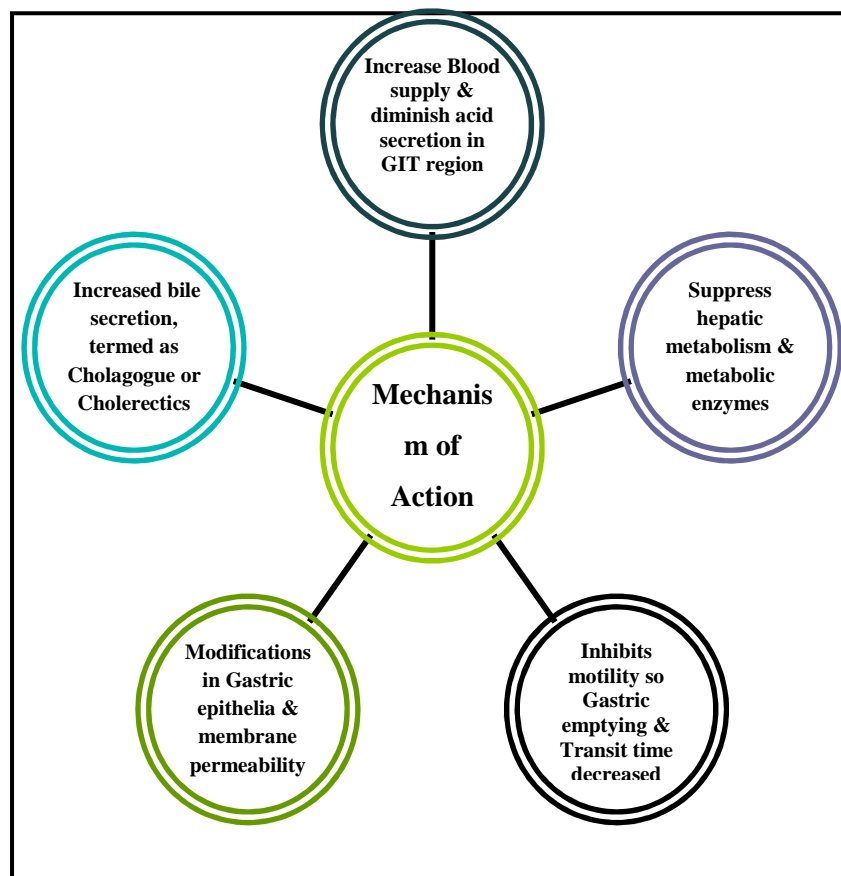


Figure 3: Common mechanism of action of Biopotentials

- **Extent of absorption:** It increases the absorption of drug molecule in gastrointestinal region because it vasodilates the tissues that results in higher extent of perfusion in the area.
- **Stimulation of gamma glutamyl transpeptidase:** GGT is important amino acid transporters found in gut region, its stimulation enhance the uptake of amino acids which ultimately enhance the absorption of drugs which conjugates with amino acid.

- **Miscellaneous:** It is assumed that piperin acts as a receptor for certain molecules or enhance the sensitivity of receptors. It also modulates cell transduction pathways so decrease the efflux signals. Modulation of dynamics of cell barrier or blood brain barrier ultimately ends in enhancement of transportation of drugs [17].

PIPERINE AND OTHER MEDICINAL PLANTS AS BIOPOTENTIERS

Piperine is primitive alkaloid which is mile stone for the field of biopotential. Chemically it is 1-piperoyl piperidine. It is obtained from *Piper nigrum* or *Piper longum* whether from stem, pods or leaf part. Piperine is generally regarded as safe (GRAS) by FDA authority. Activity of piperin is due to the conjugated double bonds in side chain part. Normal dose of piperine is approximately 15-20 mg/kg for a in a day. It increases the bioavailability, blood levels and efficacy of a number of categories and some of exclusive drugs as given below [Table 2]. Categories of enzymes and drugs are given below

Metabolic enzymes [15, 16]:- Piperine interacts and interferes both *in vitro* and *in vivo* with the metabolism and degradation related enzymes Studies have proved it as a nonspecific inhibitor of drug metabolism. Piperine inhibited number of enzymes in a series mainly related to P-gp and cytochrome P 450 family. It includes others also like

- Aryl hydrocarbon hydroxylase (Microsomal enzyme system)
- Ethyl morphine-N demethylase
- 7-Ethoxycoumarin-O-de-ethylase
- 3-Hydroxy-benzo(a)pyrene glucuronidase
- Uridine di phosphate glucose dehydrogenase (UDP-GDH)
- Uridine di phosphate glucuronyl transferase (UDP-GT)
- 5-Lipoxygenase (5-LOX)
- Cyclo-oxygenase-I (COX-I)

Antitubercular and antileprotic drugs: Rifampin or Rifampicin is the drug of first line treatment in tuberculosis and leprosy. Piperin has very vast influence on this cadre of drugs hence this concept is so much useful for lowering the dose profile and shortening the treatment. Rifampin acts on RNA polymerase and inhibits the transcription of the polymerase in human cells which is actually being catalyzed by *Mycobacterium smegmatis*. Piperine augments this activity of rifampin by several folds against RNA polymerase Piperine also stimulates the binding ability of rifampin to RNA polymerase even in resistant strains [17]. Normally the ratio used is 24:1 by weight of drug and piperin has shown a great effect on growth of tuberculosis. Combination has given so many advantages; it has decreased the dose of rifampin from 450 to 200 mg. The amount of piperine used in the range of 0.4–0.9% by weight for both categories of drugs. It also affects the other drugs like isoniazid and pyrazinamide. In a report against this has acknowledge us about antagonistic effect of piperine at higher dose, it decreases the plasma concentration of rifampin [18, 19].

Antibiotics: - The consumption of antibiotics and antimicrobials are increasing at very high rate that has cause most of immune system resistance or addicted for them. Patients have to take high dose of such drugs due to reduction in GIT absorption, uptake by pathogens and cells has decreased due to resisting efflux pumps. The major portion of the target dose remains as garbage in body fluids having no therapeutic use but causing drug resistance with time. This unused load is the reason for side effects, illness, and reduction in life expectancy [13]. Flouroquinolones and piperine in rabbits has shown augmented bioavailability due to piperin inhibits the P-glycoprotein efflux pump [10]. β - Lactam antibiotics in combination with piperine have significantly increased the bioavailability due to inhibition of microsomal enzymes system by piperine [20]. Tetracycline and piperine combinations in a clinical experiment on White Leghorn birds, it has found that piperine can reduced loading and maintenance dose and only one third of actual is sufficient attain MIC with piperine. Blood samples were collected from the wings and microbial assay is used for estimation. [21].

Chemoprevention and immunomodulatory: - Piperine reduces the aflatoxins that are responsible for several cytotoxic effects by inhibiting CYP-P450-mediated biological activation of mycotoxins into harmful ones [22]. It inhibits the lipid peroxidation phenomena so it modifies the oxidative changes in cells that results in free radicals scavenging activity [23]. It causes reduction in damage of DNA and DNA proteins. The antiapoptotic property of piperin is attributed induction of Heme-oxygenase-1. It contains pentacyclic oxindole group in it which is responsible for all these activities. [24]

Nutraceuticals: It also acts as a nutritional bioenhancer which enhances bioavailability and absorption of nutrients by acting on gastrointestinal tract [Table 1]. In a double blind cross over studies it has been revealed that herbal supplementation can increase the concentration of vitamins against placebo by 50-60%. Study suggests augmentation is due to the nonspecific mechanism & thermogenic properties of piperine [25, 26].

Table 1: List of Effected Nutraceuticals [14]

S.No	Category		Name of members
1	Vitamins	Fat Soluble	B complex vitamins and Vitamin C
		Water Soluble	β -Carotene and Vitamin A,D,E,K
2	Amino acids		Tryptophane, Phenylalanine, Leucin, Isoleucin, Lysine and Valine
3	Minerals		I, Ca, Mn, Fe, Zn, Cu, Mg and K

Zingiber officinale: - It is commonly known as Ginger. It regulates the intestinal function to facilitate absorption via mucous membrane because of active gingerly. Ginger is used in the range of 10-30 mg/kg as bioenhancer. Antibiotics like Cefadroxil (65%), Cephalexin (85%), and Amoxicillin (90%) Cloxacillin (90%), Azithromycin (90%) and Erythromycin (105%), are the drugs with respective percentage of bioenhancement caused by the herb. It works very efficiently with piperine [36, 37].

Moringa oleifera: - It is commonly known as Drumstick pods which contain Niaziridin and niazirin (Nitrile glycoside). It biopotentiates antibiotics like rifampin, ampicillin, nalidixic acid by 1.5 to 19 folds against the gram-positive bacteria It increase the intestinal absorption of Vitamin B12. Nizaridine affects the activity by 5 to 6 folds of antifungal antibiotics like Cotrimazole, an azole derivative [38].

Table 2: - Drugs effected by coadministration of Piperine

Drug	Clinical Model	Experimental assumption of action
Phenytoin/ Carbamazepine	Human subjects Immunoassay	At a high dose, piperine diminishes the elimination or metabolism that results in higher amount available. It helps in epilepsy rapidly at lower doses [27].
Pentobarbitone	Pentobarbitone induced hypnosis in rats	Significantly potentiate the sleeping time in compare with the control group due to inhibition of liver microsomal enzyme system [28].
Curcuminoids	Rats and human subjects	Curcumin gets rapidly metabolized by liver and gut enzymes. Piperine increases the bioavailability about 200%. The effect is due to inhibition of hepatic and intestinal glucuronidation [29].
EGCG* (Green tea)	In albino mice	This polyphenol showed chemopreventive activity in animal models but with piperine activity of drug has increased by 1.3 times in compared to normal treated. Mechanism works behind this concept is inhibition of glucuronidation and gastrointestinal transit time [30].
Coenzyme Q10	Double blind Cross over	Supplementation of piperine with coenzyme Q10 for long time or at a high dose only can increase the bioavailability. It is assumed that piperine follows nonspecific thermogenic or bioenergetics properties for augmentation. [31].

Nimesulide Diclofenac sodium (Peripheral)	In albino mice Writhing induced by Acetic acid	Oral administration of Nimesulide/ Diclofenac can be sum up by supplementation of piperine because it inhibits the biotransformation and significantly increase the amount of drug in plasma. Co administration can relieve the pain 1.5 times faster.
Pentazocine (Central analgesic)	In Albino Mice Tail Flick Method	Piperine combined with pentazocine showed significant increase in tail flick latency in comparison with pentazocine alone and control group follows same mechanism as with peripheral drugs [32, 33].
Fexofenadine	In rats	Bioavailability can be increased up to 2- 3times than alone drug. This action of biopotential is due to inhibition of P-glycoprotein efflux pump and delayed gastric emptying [34].
Saquinavir mesylate	Human Caco-2 cells line & male SD rats	HIV-1 protease inhibitor, in presence of piperine shows good bioavailability due to inhibition of P-gp efflux of drug from cells. This bioenhancers improves the oral bioavailability of SQN by ~ 10 folds. Human cell line mimics the intestinal barrier [35].

* EGCG: - Epigallocatechin Gallate; SQN: - Saquinavir mesylate; SD: - Sprague-Dawley

Glycyrrhiza glabra: - It is commonly known as Liquorice which contains Glycyrrhizin. It augments the inhibition of cell division with the core antineoplastics drug. Studies have revealed its effect on taxol bioenhancement; this combination is used against breast cancer. Inhibition of cell growth by taxol with glycyrrhizin was higher than the taxol alone. Studies also report its positive effects on hat glycyrrhizin transportation of antibiotics like rifampin, tetracycline, ampicillin and vitamins B1 and B12 across the gut membrane [39, 40].

Cuminum cyminum: - It is commonly known as Black cumin which contains Luteolin. It enhances the bioavailability of antifungals mainly, Zidovudine and 5-Fluorouracil. The doses used for biopotential is 0.5 to 25 mg/kg. Activity is because of Luteolin which is a

potent P-gp inhibitor [41, 42]. A similar species of cumin is known as Caraway (*Carum carvi*). Its chemical constituents found in seeds which potentiate a wide range of antibiotics, antifungal, antiviral and anticancerous drugs in animal models. The effective dose ranges from 1-55 mg/kg as per body weight. [43].

Allium sativum: - It is commonly known as Garlic which contains Allyl sulfur or Allicin as bioactive fraction which highly augments and potentiates the availability of drug in blood. It augments the sensitivity of cells towards fungicidal action of Cu²⁺ ions. Amphotericin B exhibit high fungicidal activity if supplemented with allicin against *Candida albicans*, *Saccharomyces* and *Aspergillus* [44, 45].

Quercetin: - Citrus fruits are good source of this chemical. It inhibits CYP3A4 and P-gp both. It increases bioefficacy and blood levels of a number of drugs including Calcium channel blockers (verapamil, diltiazem) antineoplastics (paclitaxel, doxorubicin), digoxin and Epigallocatechin Gallate (EGCG) from the gastro intestinal tract. [46-48]

Ipomoea species: - It is commonly known as Morning glory plant which contains Lysergol. It enhances the bactericidal activities of different antibiotics [14].

Aloe barbedensis: - It is commonly known as Indian Aloe which contains Aloein and Emodin they are responsible for improvement of the absorption of both the vitamin C and E.

The absorption gets slower and vitamins last longer in the plasma with aloe, this increases bioavailability of Vitamin C and E in human. Aloe Vera is a very promising because its future nutritional and medicinal value as herbal bioenhancer [49].

Genistein: - It belongs to isoflavones category and a well known herbal estrogen. Genistein is reported to be able to inhibit P-gp, BCRP and MRP-22 efflux function. When it is administered with genistein the intestinal absorption of paclitaxel is dramatically increased only at small dose of 10 mg/kg [50, 51].

Sinomenium acutum: - It is a Chinese herb which produces an alkaloid Sinomenine. This herb belongs to Menispermaceae. This alkaloid can decrease the efflux transport and increase the disposition time of paeoniflorin by inhibiting P-glycoprotein mediated cellular pumps in rats. This combination can be useful in the treatment of inflammation and arthritic [52, 53].

Naringin and Naringenin: - They are basically flavonoid glycoside found in grapefruit and makes grapefruit juice taste bitter. Oral naringin dose is 10 mg/kg of body weight .It has great effect on doxorubicin, paclitaxel, verapamil and tamoxifen also. In case of tamoxifen it inhibits CYP3A4enzyme that makes drug more bioavailable [54-56].

Callistemon rigidus: - A bioactive fraction encoded as F₅obtained from leaves was found to be active against ciprofloxacin-resistant microbes at a very low concentration with main drugs in treatment. It has demonstrated powerful synergistic action with resistant drugs against mutant strain of *S. aureus* [57].

Capsicum annum: - It is commonly known as Chili pepper which gives Capsaicin which enhances the bioavailability theophylline and ciprofloxacin. In an experiment on rabbits oral dose of theophylline with or without Capsaicin has given the second maintenance dose of bioenhancer after 11 hours raised the plasma levels of theophylline [58, 59].

Stevia rebaudiana: - It is commonly known as Stevia or honey leaf which contains mainly stevioside, a glycoside. Other constituents include steviol and rebaudioside. Extract of Stevia in combination with piperine is highly selective in enhancing bioefficacy of many of drugs, nutraceuticals, and polyherbal formulations. The percentage weight used ranges from 0.01 to 80% as per weight formulation. The dose of Stevia used in formulation is ranges from 0.01 to 50 mg/kg body weight [60, 61].

Biopotentiars: Animal origin

Normally most of bioenhancers are of herbal origin but one of them is of animal origin and highly useful as biopotentiars with its own miraculous pharmacological effects alone.

Cow Urine: - Cow urine is very effective as a biopotentiars but its distilled form is more used than normal urine. It increases the bioefficacy of antimicrobial, antifungal, and anticancer agents [62]. Cow urine has antitoxic activity itself and if used as augmenting agent with zinc against the cadmium chloride toxicity, it shows miraculous effects. In an experimental study mice treated with cadmium showed zero fertility. But on the other side when a group is treated with cadmium (Anti fertility agent), zinc (Core drug) and cow urine distillate (Biopotentiars) showed high fertility index. This indicates that it can be used as a bioenhancer of zinc in cadmium fertility toxicity [63]. It also increases the activity of Rifampicin against *Escherichia coli* and gram positive bacteria. Mechanism of action of bioenhancing is increased transport across the GIT membrane. The enhancement in transport is approximately 2–7 times. Cow urine distillate enhances both the release an activity gonadotropin releasing hormone (GRH) ultimately increase sperm motility, sperm count, and sperm morphology in male mice [64].

CHALLENGES AND HURDLES

Challenges have been encountered while the development of the concept of biopotentiation, to modify the physicochemical virtues of the drug likes drug degradation and crossing of biological barriers. Large scale production of such agents is very much essential for commercialization of this concept. Such agents are used at very low concentration in process so it is easy to improved performance at laboratory scale rather at large scale. When the scale up starts it is a hurdle to maintain bioenhancers composition. New challenges for regulatory controls are also there. The FDA (United states) and the European Medicines Evaluation Agency (EMA) are the first to come up with regulation for bioenhancers and nanomaterials. [65].

SUMMARY AND CONCLUSION

Ayurveda + Allopath = Multidirectional benefits

India is a country where the Ayurveda has taken birth but at other side costly. Allopathic modernization is all about novel chemical entities with new mode of action that affects cost of development. Reverse pharmacology is a revolutionary breakthrough to identify active therapeutic agents at minimal cost of drug discovery.

Scientific society has their eagle eyes on reduction of cost of dosage and indirectly the whole treatment, cost effective and cheap allopathic cure can be provided to each and every cadre of society whether they are not financially sound. The effective strategy is to optimize the pharmacokinetic parameters such as bioavailability of expensive drug so at minimal dose it impacts in disease. Biopotentiality using nature originated agents have significantly enhanced the bioavailability profile of so many poor oral bioavailable drugs. Herbs from nature include *Piper longum* or *nigrum*, *Zingiber officinale*, *Aloe barbedensis*, *Sinomenium acutum*, *Glycyrrhiza glabra*, *Moringa oleifera*, *Cuminum cyminum*, *Carum carvi*, *Allium sativum*, *Capsicum annum*, *Stevia rebaudiana*, *Ipomoea species* and juices from citrus and grapefruits. Animal originated cow urine distillate is also a milestone in this cadre of medicinal field. They have decreased the usual dose of potents and nutraceuticals so ultimately reduced the drug-resistance, toxicity and shortens the period of treatment. This integration of tradition and technology satisfies all necessary criteria of safe and ideal combination. This coadministration of herbal bioenhancers with synthetic drugs is effective, economical, and easy and covered each an every class of drug. The current paper has discussed the potentiating activity of herbal or natural biopotentials of drugs in animals and humans but these compounds have not been completely explored in vivo till date and still adhered with lack of information on their exact mechanism of action, toxicities evaluation of extracts, and suitable combinations.

FUTURE PRACTICES

Ayurveda leads the modern researcher to find their way with candle. Most of allopathic molecules almost 70% could be traced back to nature. It has started from the first concept of Yogvahi using "Trikatu" as a bioenhancer in ayurveda which was further applied successfully to various modern medicines. The ayurvedic concept of Anupaan and Sehpaan need to be merged with into the modern medicine also for healthy effects. Safe medicines with safer routes of drug administration bifurcated only by the hole of ayurveda and allopathic system in future also. Some of area of bioenhancement is still need to lighten up and highly focus on their active principles, mechanisms of actions, clinical outcomes, toxicities evaluation, and suitable combinations with other drugs. So we can explore novel principles with high bioenhancing ability and less toxic effects.

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