Title- A Review on Herbal Bioenhancer

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ABSTRACT

Ayurveda has made a major contribution to the drug discovery process with new means of identifying active compounds. Recent advancement in bioavailability enhancement of drugs by compounds of herbal origin has produced a revolutionary concept in the way of therapeutics. This concept was known as yogvahi in Ayurveda. Herbal bioenhancers have been shown to enhance bioavailability and bio efficacy of different classes of drugs such as antibiotics, antituberculosis, antiviral, antifungal, and anticancer drugs at low doses. They have also improved oral absorption of nutraceuticals like vitamins, minerals, amino acids, and certain herbal compounds. Bioenhancers 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. The need for bioenhancers arises due to drugs which are poorly available, administered for long periods, toxic and expensive. The objective of this review is to summarize up to date information of natural bioenhancers.

Keywords-Bioenhancer, Yogvahi, Ayurveda, Modern medicine, bioavailability

INTRODUCTION

Drugs that are administered orally go through a dissolution process and then permeation across the gastric membrane before they can appear in the blood stream. The amount of drug that goes into the bloodstream from its site of administration is defined as its bioavailability . Solubility is defined as the property of a substance to dissolve itself into a solid, liquid or a gaseous solvent to form a homogeneous solution of it. Solubility of a drug in gastric media is an essential requirement for an orally administered drug to be absorbed adequately . The majority of factors that affect the bioavailability of a drug other than solubility and permeability include the dissolution rate of the drug, first-pass effect, pre-systemic metabolism of the drug in any other organ and susceptibility to efflux mechanisms. Solubility in the gastric media is a major problem associated with orally administered drugs that leads to erratic bioavailability and possible toxicity in the living system; making solubility of new drug molecules one of the crucial challenges for formulation scientists. In spite of these issues, the oral route of drug administration has been the most sought after route due to its ease of administration, high patient compliance, cost-effectiveness, least need for maintenance of sterile conditions, and flexibility in design of enzymes. The use of bioenhancers is a promising approach to overcome the issues related to bioavailability. A bioenhancer enhances the bioavailability of a drug molecule without causing any pharmacological activity of its own. Bioenhancers of herbal origin have gained interest recently and many herbal compounds including quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin and nitrile glycoside have proved their efficacy in increasing the bioavailability of the drugs with which they are combined.

I. Barriers to Drug Absorption For a drug to exert its biological actions, it is essential for it to reach to the systemic circulation. However, the drug has to cross various biological barriers before it reaches to the bloodstream. The epithelium of intestine consists of several physiological barriers to the absorption of drug. Solubility and permeability of a drug are important barriers to its absorption. The aqueous layer present on the intestinal epithelium serves as a crucial barrier for the absorption of drugs due to their hydrophilic nature . Generally, drugs with size more than 0.4 nm seldom pass through the aqueous channels. Results from recent investigations have also revealed that P-glycoprotein, a type of energy dependent efflux pump plays important roles in preventing the entry of drug into systemic circulation. The presence of both Cytochrome P450 (CYP) 3A and P-glycoprotein and their combined action on the enterocytes is also assumed to be a limiting factor in oral drug absorption . Importantly, the inhibition of these proteins have shown enhanced bioavailability of drug in clinical studies .Moreover, the thick cytoplasm of the cells responsible for the absorption is also acts as a potential barrier to the transfer of drug from the site of absorption to the systemic circulation .

II. What Are Bioenhancers A herbal bioenhancer is an agent of herbal origin that has the capability to enhance that bioavailability of a drug with which it is combined, without causing any pharmacological activity of its own (13).Adding a bioenhancer to a drug helps to reduce drug dosage, drug cost, incidences of drug resistance and risks of adverse drug reaction. Most importantly, a bioenhancer improves the efficacy of a drug by enhancing its bioavailability. In addition, adding a bioenhancer also reduces raw material requirement during pharmaceutical manufacturing. Major categories of drugs that have shown increased bio enhancement include the drugs acting on cardiovascular system (CVS), respiratory system, central nervous system (CNS), gastrointestinal tract(GIT), antibiotics and anticancer agents. Some examples where addition of bioenhancers have significantly improved the drug efficacy include tetracyclines, sulfadiazine, vasicine, rifampicin, isoniazid, pyrazinamide, ethambutol, phenytoin, phenobarbitone, carbamazepine, nimesulide, indomethacin beta-carotene, coenzyme Q10 (CoQ10), ciprofloxacin, curcumin, dapsone, amino acids, glucose and several other classes of drugs(6Origin of Bioenhancers: Bioenhancers is an ancient term of “Ayurveda” which implies the increase effect of drug in combination with it. Ayurveda terms it as “Yogvahi” in Sanskrit which indicates increase in effect by combination. There are two concepts related to Yogvahi

1. Anupaan: in which yogvahi is given with the food to increase its effect.

Eg. Amritdhara drops Used in gastrointestinal diseases, by putting drops over sugar to increase potency.

2. Sehpaan: means vehicle, which is used during manufacturing of medicament.
In 1929, Bose has documented action of bioenhancer. He has used long paper to increase antihistaminic property of vasaka. Another scientist C. K. Atal has scientifically estimated piperine as first bioenhancer in 1979, work is done at Regional Research Laboratory, Jammu (Indian Institute of Integrative Medicines) in ayurveda Trikatu i.e. black paper (Piper nigrum), long paper (Piper longum) and ginger (Zingiber officinale) is used widely, so Mr. Atal put hypothesis that Trikatu increases efficacy. When he studied all ingredients, he found piperine i.e. active constituent in Piper longum increases bioavailability of many drugs, so according to its work to enhance bioavailability bioenhancer‟ term was coined.

NOVEL PROPERTIES OF BIOENHANCERS

These bio enhancers have different property, but they have some special property whichis required to give their bio enhancingactivity and these novel properties are as follows:

1. Nontoxic to humans or animal.
2. Should be effective at a very lowconcentration in a combination.
3. Should be easy to formulate.
4. Enhance uptake or absorption.
5. Enhance activity of drug molecule.

MECHANISAM 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 by enhancing the supply of blood.
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. Bio enhancers in such case act by inhibiting the P-gp.
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 reabsorption
Few other postulated theories for herbal bio- enhancers are
6.Reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply.
7.Inhibition of gastrointestinal transit, gastric emptying time and intestinal motility.
8.Cholagogoue effect.
9.Bioenergetics and thermogenic properties.
10.Suppression of first pass metabolism and inhibition of drug metabolizing enzyme and stimulation of gamma glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids.[4,5]

HURDLES IN BIOENHANCER

1. One of the challenges is to improve on properties of drug formulations such aslonger duration of circulation in blood,enhanced surface area, protection of incorporated drug from degradation, crossing of biological barriers and sitespecific targeting.
2. Other challenge is large scale production.
3. The challenges of scaling up involve small amount of Nano-materials, agglomeration and the chemistry process.
4. In bio enhancers the advances also bring different challenges for regulatory control.

CLASSIFICATION OF BIOENHANCER
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

Plant origin	Animal origin
Eg. Capsaicin, Ginger, Aloe Vera, Curcumin, Stevia, Genistein, Naringin, Caraway, Turmeric, Pepper, Peppermint oil	E.g. Cow urine distillate (Kamdhenu ark).

Table 2-Based on mechanism of action

Inhibitors of P-gp effluxpump and other efflux pump	Suppressors of CYP-450enzyme and its isoenzymes	Regulators of GIT function to facilitate better absorption
E.g. Caraway, Genistein, Sinomenine, Black Cumin, Naringin, Quercetin	E.g. Naringin, Gallic acidand its ester, Quercetin.	E.g. Aloe Vera, Niaziridin, Ginger, Liquorice.[5]

NATURAL PRODUCTS AS BIOENHANCERS

Resveratrol

Resveratrol (3,4′,5- trihydroxystilbene) is a nutraceutical that has recently attracted a lot of research attention due to its exciting
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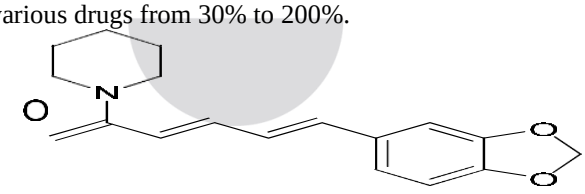
Resveratrol (3,4′,5- trihydroxystilbene) is a nutraceutical that has recently attracted a lot of research attention due to its exciting pharmacological potential. It is a phytoalexin found in many plants including red wine, grapes, peanuts, and berries. Coadministration of apigenin and resveratrol led to a 2.39 fold increase in plasma apigenin levels compared to administration of apigenin alone. Resveratrol inhibits the formation of apigenin glucuronides by inhibiting UGT1A9 enzyme in a non-competitive manner.

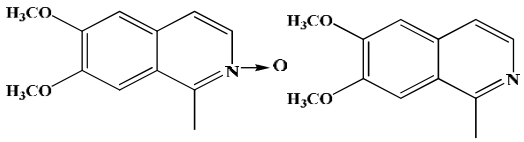
Piperine

Piperine is a major alkaloidal component of Piper nigrum Linn. (Piperaceae). Piperine, or mixtures containing piperine, has been shown to increase the bioavailability, blood levels and efficacy of a number of drugs including vasicine, sparteine, sulfadiazine, rifampicin, phenytoin and propranolol.22, 23 Piperine act by suppressing P-gp and cytochrome P450 enzymes, which counteract the metabolism of rifampicin via these proteins, thus enhancing the oral bioavailability of rifampicin. It also decreases the intestinal production of glucuronic acid, thus allowing more substances to enter the body in active form. It was found to increase the bioavailability of various drugs from 30% to 200%.



Black Cumin

Nigella sativa (Black cumin) belonging to family Ranunculaceae. It is extensively used in the Indian diasporas as spice, which may interact with co-administered drugs and affect their intestinal availability. In the in-vitro study methanolic and hexane extracts of Nigella increased the permeation of amoxicillin significantly. In in-vivo experiments black cumin enhanced amoxicillin bioavailability. C max of amoxicillin increased in rat plasma when administered orally alone and in combination with hexane extract correspondingly from 4138.25±156.93 to 5995.04±196.28 ng/ml while as AUC0→t increased from 8890.40±143.33 to 13483.46±152.45 ng/ml.h.



Glycyrrhizin

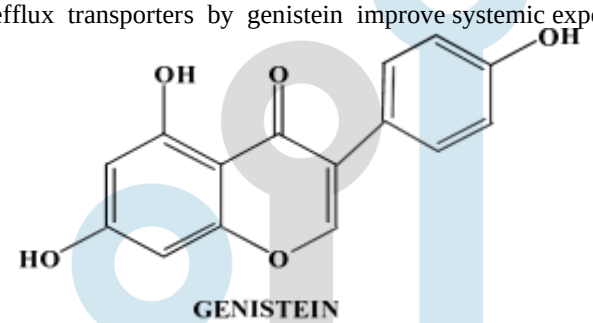
Glycyrrhizin is a triterpenoid saponin found in Glycyrrhiza glabra Linn. (Leguminosae). The absorption-enhancing activity of sodium deoxycholate and dipotassium-glycyrrhizinate was much greater when administered with glycyrrhizin. The absorption enhancing activity of glycyrrhizin was increased by presence of other absorption enhancers. Glycyrrhizin showed a more potent absorption enhancing activity than caproic acid at the same concentration tested.

Cumin oil

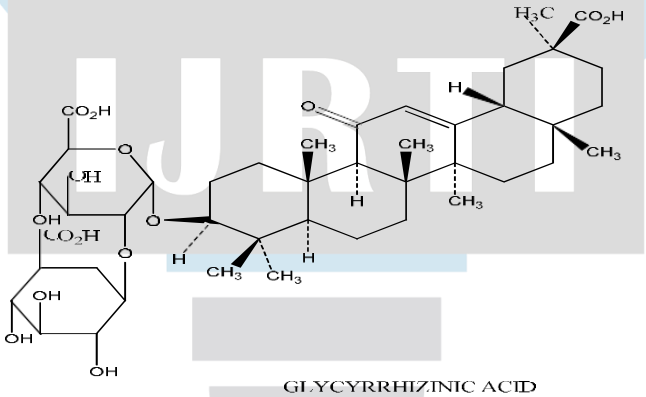
Cuminum cyminum Linn. (Apiaceae) is an annual herb, its fruits are generally used as spice. Cumin oils and its bioactive compound like luteolin seemed to attribute the bioavailability enhancing activity. Luteolin has been reported to be a potent P-gp inhibitor.27 Bioavailability enhancing activity of C. cyminum was revealed toward a number of drugs.

Genistein

Genistein, well known as a phytoestrogen29 inhibits P-gp, Breast Cancer Resistance Protein (BCRP) and Multidrug Resistance-Associated Protein 2 (MRP2) efflux function. The intestinal absorption of paclitaxel, a substrate for efflux transports such as P-gp, BCRP and MRP2 considerably increased when co-administered with genistein. It has been reported that the inhibition of the efflux transporters by genistein improve systemic exposure of paclitaxel.



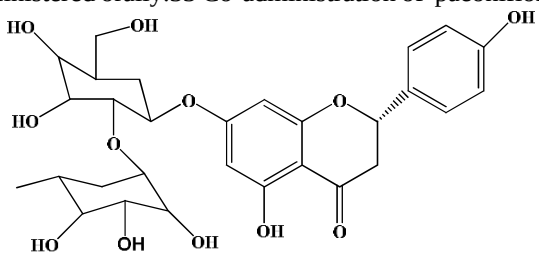
GENISTEIN



GLYCYRRHIZINIC ACID

Naringin

Naringin is the major flavonoid glycoside found in grapefruits, that shows the inhibition of P-gp and CYP3A in rats.31 Area under curve (AUC) of paclitaxel is increased significantly in presence of naringin (49.1% for naringin at 10 mg/kgSinomenine, an alkaloid extracted from Sinomenium acutum (Menispermaceae). Paeoniflorin, bioactive monoterpene glucoside has a poor bioavailability (3-4%) when administered orally.33 Co-administration of paeoniflorin with sinomenine, the AUC of paeoniflorin

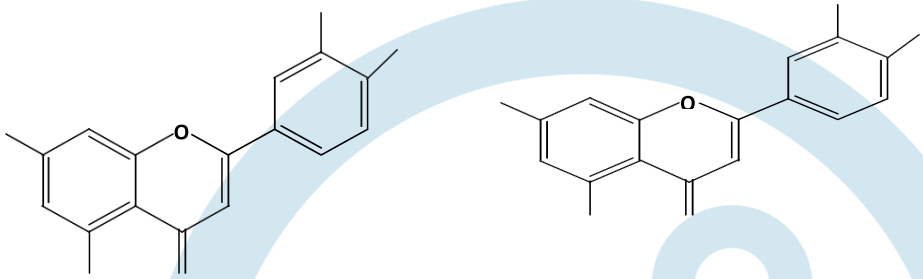


NARINGIN

significantly increased, thus the oral bioavailability of paeoniflorin was enhanced by more than 12 times in rats treated with sinomenine.

Quercetin

Quercetin is a flavonoid found in Citrus fruits. It is reported that quercetin increase bioavailability, blood levels and efficacy of a number of drugs such as diltiazem, digoxin and epigallocatechin gallate. The absorption of epigallocatechin gallate has been enhanced with red onion supplementation, which is a rich source of quercetin. The AUC of epigallocatechin gallate determined over a period of 6 h increased from 1323 to 1814ng.h/ml, when co-administered with quercetin.



Peppermint

Peppermint oil extracted from Mentha species contains mainly menthol and menthone. Co-administration of cyclosporine and Peppermint oil, it increased cyclosporine maximum concentration (Cmax) and area under the concentration versus time curve (AUC0-a) from 0.60 to 1.6 µg/ml and 8.3 to 24.3 µg.h/ml, respectively in in vivo experiment.

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Nitrile Glycosides

Nitrile glycosides and its derivatives such as niazirin and niaziridin is obtained from the leaves, pods, and bark of Moringa oleifera (Moringaceae). These glycosides enhanced the absorption of commonly used antibiotics such as rifampicin, Ztetracycline and ampicillin, vitamins and nutrients.

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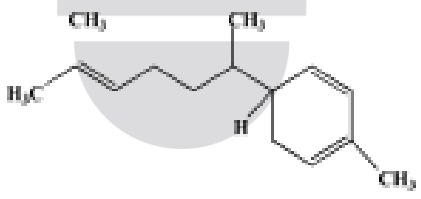
Ginger

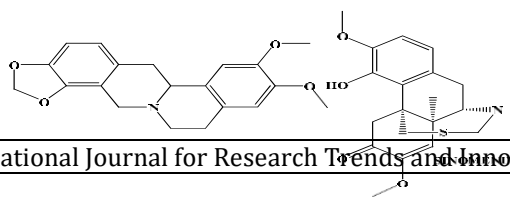
zingiber officinale (Zingiberaceae) is one of the components of Trikatu which also possess significant bioavailability enhancement activity.41 Ginger mainly contains zingiberene, gingerol and shagol. Gingerols and shagols are responsible for pungency of Ginger. It has a powerful effect on mucous membrane of the gastrointestinal tract. It regulates the intestinal functions to facilitate absorption. Ginger when used in the dose of 10–30 mg/kg body weight acts as bioenhancer. Pharmacological studies shows that it dramatically enhanced the bioavailability of various medicines especially antibiotics such as amoxicillin, azithromycin, erythromycin, cephalexin, cefadroxil, and cloxacillin.



ZINGEBERENE

Sinomenium acutum

Sinomenium acutum: The mechanism underlying the increase in bioavailability of paeoniflorin is explainedas sinomenine could decrease the efflux transport of paeoniflorin by P-gp in the small intestine. There are various chemical constituents [Fig-12] in this plant responsible for bio enhancing action are: isotertrandrine, curine, sinactine,sinomenine, magnoflorine.



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There are various herbal formulations are available which are act as bio enhancers and they are present in plant source which show there bio enhancing action by different mechanism. The herbal formulations which are used as bio enhancers are as follows: Herbal liposomal formulation (Table 3), transferosome (Table 4), microsphere (Table 5), nanoparticles (Table 6), and lipid based herbal formulation (Table 7), recent patent on herbal controlled release formulations.

Table 3-Herbal liposomal formulation

Formulation	Active ingredient	Application	Method of preparation	% entrapment efficiency	Route of administration
Quercetin liposome	Quercetin	Lower dose, improved dispersion in BBB	Reverse evaporation technique	60%	Intranasal
Liposome encapsulated silymarin	Silymarin	get better bioavailability	Reverse evaporation technique	69.22%	Buccal
Liposome Artemisia arboresens	Artemisia arboresens	Targeting of essential oils to cells	Film method and sonication	60-74%	In-vitro
Ampelopsin liposome	Ampe-lopsin	Increase efficiency	Film ultrasound method	62.90%	In-vitro
Paclitaxel liposome	Paclitaxel	Efficiency of high entrapment	Thin film hydration method	94%	In vitro
Curcumin liposome	Curcumin	Long circulation withhigh trap efficiency	Ethanol injection method	88.27%	In-vitro
Garlicin liposome	Garlicin	Increase efficiency	Reverse phase evaporation	90.77%	In-vitro

Table 4-Transferosomes:

Formulation	Active ingredient	Application	Biological activity	Droplet size	Route of administration
Capsaicin transferosomes	Capsaicin	Increase skin penetration	Analgesic	150.6 nm	Topical
Colchicine transferosomes	Colchicine	Increase skin penetration	Antigout	-	In-vitro
Vincristine transferosomes	Vincristine	Increase entrapment efficiency andskin Penetration	Anticancer	120 nm	In-vitro

Table 5-Nanoparticles

Formulation	Active ingredient	Application	Biological activity	Method of preparation	% entrapment efficiency	Route of administration
Triptolide nanoparticles	Triptolide	Enhance the penetrationof drug	Antiinflammatory	Emulsification ultrasound	-	Topical
Nanoparticle of cascuta chinensis	Flavonoid and lignans	Improve water solubility	Hepato-protective and antioxidant activity	Nano suspension method	90	Oral
Artemisinin nanocapsules	Arteminin	Sustained drug release	Anticancer	Self- assembly procedure	90-93	In-vitro
Radsalvia miltriorrhiza nanoparticles	Radix salivia	Better bioavailability	angina pectoris, Coronary heart diseases, myocardial infraction	Spray drying technique	96.68	In-vitro
Taxol loaded nanoparticles	Taxol	Develop bioavailability	Anticancer	Emulsion solvent evaporation	99.44	In-vitro

Table 6 -Microspheres

Formulation	Active ingredient	Application	Biological activity	Method of preparation	Size in mm	Route of administration
Rutin-alginate chitosan microspheres	Rutin	Targeting into cardiovascular & cerebro- vascular system	Cardiovascular and cerebrovascular	Complex coacervation method	165-195	In-vitro
Zedoary oil microspheres	Zedoary	Sustained release and higher bioavailability	Hepato-protective	Quasi emulsion solvent diffusion method	100-600	Oral
CPT loaded microspheres	Camptothecin	Prolonged release of camptothecin	Anticancer	Oil in water evaporation method	10	Intraperitoneal or intravenously
Quercetin Microspheres	Quercetin	Significantly decreases the dose size	Anticancer	Solvent evaporation	6	In-vitro

Table 7-Lipid based herbal formulation

Formulation	Active ingredient	Application	Biological activity	Method of preparation	Dose	Route of administration
Ginkgo biloba lipid based systems	Flavonoids	Stabilizes ROS	Cardio protective and antioxidant activity	Phospholipidc omplexation	100mg	Subcutaneous
Silybin lipid based systems	Flavonoids	Inhibit lipid peroxidation	Hepatoprotective and antioxidant	Phospholipidc omplexation	120mg	Oral
Ginseng lipidbased systems	Flavonoids	Increases absorption	Nutra- ceutical immune modulator	Phospholipidc omplexation	150mg	Oral
Green tea lipid based systems	Ginsenoside	Increases absorption	Neutraceutical	Phospholipidc omplexation	50-100mg	Oral
Grape seed lipid based systems	Epigallocatechin	Increases absorption	Systemic antioxidant	Phospholipidc omplexation	50-100mg	Oral
Hawthorn lipid basedsystems	Procynidins	The blood TRAPn Significantly elevated	Cardio-protective, anti-hypertensive	Phospholipidc omplexation	100mg	Oral
Quercetin lipid basedsystems	Flavonoids	Exerted better therapeutic efficacy	Antioxidant and anticancer	Quercetin Phospholipid complexation	50-100mg	Oral

Table 8-Recent patents on herbal controlled release formulations:

US patent number	Active ingredient	Novel system incorporate
US 5948414	Opioid analgesic and aloe	Nasal spray
US 6340478 B1	Ginsenosides	Microencapsulated and controlled release formulation
US 6890561 B1	Isoflavones	Microencapsulated formulation
US 6896898 B1	Alkaloids of aconitum species	Transdermal delivery system
US patent 2005/0142232 A	Oleaginous oil of Sesamum indicum and alcoholic extractof Centella asiatica	Brain tonic

US patent 2007/0042062 A1	Glycine max containing 7sglobulin protein extract, curcumin, Zingiber officinalis	Herbal tablet dosage form
US patent 2007/0077284	Opioids analgesics (phenanthrene gp)	Transdermal patch
US patent 7569236132	Flavonoids and terpenes	Microgranules

APPLICATIONS

These techniques of bio enhancers is principally targeted the toxic drugs, expensive drugs, rare drugs, poorly bio- available drugs and the drugs which are used for longer duration. However, it can also be used in any drugs influenced by bio enhancers. The innovation and explanationof bioavailability enhancers has lead toseveral patent applications. Piperine is marketed as mono-preparation bio enhancer and as a constituent of nutritional additivethat contain different vitamins, curcumin resveratrol or coenzymes.

Since bio enhancers can reduce the dosage and cost of expensive medication while making treatment safer, in humans first time its application has been done in treating TB for which the existing drugs are toxic and expensive and they are administered for longer period. Country like India where low treatment costs for health check care are essential. The drug risorine is approved against TB.

CONCLUSION

Natural bioenhancers leads an innovative concept in the drug discovery. They will lead to reductions in drug cost, toxicity, adverse effects and enhances therapeutic efficacy or bio efficacy. New chemical substances with new modes of action are what modern pharmaceutical research is all about. Drug discovery process is highly aided by different system such as ayurveda through reverse pharmacology with new means of identifying active compounds. Research aimed at developing novel and powerful bioenhancers such as Resveratrol and Piperine and their derivatives and increase the bioavailability in systemic circulation.

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They will lead to reductions in drug cost, toxicity, adverse effects and enhances therapeutic efficacy or bioefficacy. Research aimed at developing novel and powerful bioenhancers such as Resveratrol and Piperine and their derivatives conti