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Review Article

Herbal Bio-Actives : A Key for Bioavailability Enhancement of Drugs

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Abstract *- Background: In recent years, there has been a major interest and medical need for the enhancement of the bioavailability of several drugs which are poorly bioavailable. Poorly bioavailable drugs remain sub-therapeutic because a considerable portion of a dose never enters the plasma or exerts its pharmacological action unless and until very large doses are delivered. bioenhancers play a key role in raising the bioavailability and efficacy of a variety of pharmacological drugs at minimal doses.*

Main Body: The present work's main goal is to review bioenhancers, their modes of action, characteristics, classification, overview, and formulation in the market of bioenhancers. Importance of Fulvic Acid, Gelucire, Naringin, Esters of gallic acid, Cumin, Ginger, Caraway, Piperine, Sinomenine, Genistein, Lysergol, Cow urine distillate, Nitrile glycoside, Glycyrrhizin, Capmul, Gokhru and, Aloe vera gel as bioenhancers.

Conclusion: The various bioenhancers, emphasizing their distinct modes of actions, applications, and their safe dose and drugs bio-enhanced by them. It also focuses on the most recent breakthrough notion of using bio-enhancers to improve the bioavailability/bio-efficacy of low-bioavailability medications, metals, nutraceuticals, and vitamins through various techniques. Therefore, Extensive research on these bio-enhancers should be carried out so that they can be utilized in drug formulations.

Keywords *- Bioenhancer, Bioavailability, Bio-efficacy, Herbal, Bio-actives.*

1. Introduction

Bioenhancers are natural or chemical moieties that enhance or promote the rate of a drug's bioavailability when used with them but do not have a synergistic action with the drug. They work through several processes that can affect the drug's metabolism, absorption, and target action.[1] The current focus of researchers in the lower therapy expenses, will make treatment more feasible for those who are financially challenged. Because India is a developing country, therapy expenses for new allopathic drugs are a major concern. Innovative approaches for lowering drug costs are urgently required as, internationally, billions of dollars are being spent annually due to drugs that are poorly bioavailable.[2,3] For example, The invention of piperine as a bioenhancer in 1979 introduced a new notion into research, with the administration of piperine dramatically increasing the blood levels of propranolol, rifampicin, phenytoin, sparteine, sulfadiazine, theophylline, and tetracycline in humans.[4] Taxol is used to treat breast cancer. This drug is extracted from the Yew, a slowest growing tree in the world, and to obtain taxol for one patient, six trees of 25–100 years are needed to be chopped. But instead, combining a bioenhancer with taxol means that lesser trees will be chopped lead which will come out as a benefit for the ecology. [4] Along with this, the research on expensive, poisonous, scarce, and poorly bioavailable drugs necessitates the application of an ideal bioenhancer that is safe, effective, affordable, easy to obtain, non-addictive, and so on. Comprehensive research on these bioenhancers is critically needed so that they can be utilized in drug formulations in the future.[2]

2. What is Bioavailability

Bioavailability refers to the pace and extent to which a bioactive drug enters the systemic circulation and therefore becomes available at the desired site of action. Drug absorption is inconsistent and partial on oral administration. Before reaching the bloodstream, the first pass effect destroys a considerable part of the pharmacologically active

drug. The approaches for increasing drug bioavailability also raise drug levels in the bloodstream and thus the efficacy. As a result, the amount of medicine needed to produce a certain therapeutic effect is reduced. Therefore, the drug dosage required to achieve a certain therapeutic effect is reduced. Physical methods such as active drug solubilization, micronization, crystal form selection, site as well as timed-release preparations, and various nanotechnology methods have previously been utilized to enhance the drug bioavailability in a limited manipulation framework.[2,3]

3. History of Bioenhancers

The notion of natural herbal bioenhancers has a history that could be dated back to the Ayurvedic medicine system's ancient knowledge. The term for this concept in Ayurveda is "yogvahi," and it is utilized to promote the therapeutic effect of drugs by increasing their tissue distribution, enhancing their bioavailability through the oral route, lowering their dose and harmful effects, and avoiding parenteral drug administration. Since the 7th century. Through the 6th century, people used the ayurvedic treatment "Trikatu," a Sanskrit term that means "three acrids." It contains the combination of black pepper (Piper nigrum), long pepper (Piper longum), and ginger (Zingiber officinale) that contains the active principle piperine, which enhances the bioavailability of drugs, nutrients, and vitamin absorption. Bose introduced the notion of bioavailability enhancers in the year of 1929 when he detailed how adding long pepper to leaves of Vasaka increased its anti-asthmatic benefits. At the Indian Institute of Integrative Medicine in Jammu, Indian scientists were the first to coin the phrase “bioavailability enhancer”. In 1979, they developed piperine, the world's first bio enhancer, and scientifically confirmed it.[1]

4. Modes of action of Bioenhancers

Several modes of action are used by bioenhancers. Nutritional bioenhancers act on the GI tract to promote absorption. Few bioenhancers work by inhibiting antimicrobial drugs from being metabolized. The following are proposed modes of action for bioenhancers

- Increases the drug's bioavailability throughout the GI tract's membrane.
- The enzymes involved in drug metabolism are inhibited, lengthening the final period of action.
- By enhancing the drug's impact via conformational interaction.
- They could behave as self-receptor for medicinal compounds.
- Active drugs are engineered so that they become responsive to their target locations.
- P-glycoprotein activity on the luminal membrane is inhibited.
- Increased mobility of gut brush border membrane, resulting in weakening of the physical barrier.
- Reducing gastric acid secretion.
- Time of Gastric emptying is reduced.
- Motility of the intestinal tract is reduced.
- Modulation of the permeability of the gastrointestinal mucosal cell membrane.
- The cholagogic effect.
- Thermogenic and bioenergetic characteristics change.
- Renal clearance is inhibited by avoiding the presence of drugs in glomerular filtration, lowering tubular secretion by P-glycoprotein inhibition, and increasing the passive tubular reabsorption.
- By Inhibiting First-pass metabolism.
- Amino acid absorption is aided by increased glutamyl transpeptidase (GGT) activity.
- Because of the drug's immunomodulatory properties, the dose has been reduced.
- The penetration level is enhanced to the point where it can access pathogen persistors within macrophages, such as Mycobacterium tuberculosis. This approach finally ensures the eradication of these organisms from areas where active medicine would otherwise be inaccessible.
- Altering infections or aberrant tissues’ ability to reject the treatment, such as efflux transporter mechanisms commonly seen in antibacterial, antimalarial, and anticancer drugs. The signaling process between the pathogens and the host is altered, allowing drugs to enter the pathogens more easily.
- Therapeutic drugs bind better and longer to target areas, including DNA, RNA, receptors, and proteins potentiating and extending their therapeutic impact against microbes. [2]

5. Characteristics of Bioenhancers

- It should not have any of its own pharmacological effects.
- Should exhibit reproducible and predictable activity.
- They must be non-irritating, non-toxic, and non-allergenic.
- They must be rapid-acting.
- The action of bioenhancers must be one-directional.
- They must be cost-effective.
- Compatibility of bioenhancers with the pharmacologically active ingredient (API’s) is essential.
- They must be capable of being easily formulated into different dosage forms.
- They must be readily available and should be stable throughout.[5]

Table 1. Overview of Bioenhancers shows the various herbal sources of bioenhancer, their action, and safe doses

Sr. No.	Drug /Source	Bioenhancer	Mechanism of action	Route of administration	Drug Bio-enhanced	Safe dose	Reference
1	Cuminum cyminum	Cumin	Inhibition of the p-gp efflux pump	Oral	Rifampicin Cycloserine Ethionamide Cefadroxil Cloxacilin Fluconazole Zidovudine	0.5-25 mg/kg body	1
2	Rhizome or stem of *Zingiber officinale*	Ginger	By regulating GI tract function	Oral	Rifampicin Ethionamide Azithromycin, Ketoconazole, Zidovudine	10- 30 mg/kg body	4
3	Persian cumin /Meridian Fennel	Caraway	Modulation of local mucosal tissue	Oral	Rifampicin Isoniazid Pyrazinamide	1-55 mg/kg of body weight	4,7
4	Morning Glory (*Ipomoea spp*.)	Lysergol	Metabolism Inhibition/Efflux Transporter (BCRP} inhibition.	Oral	Berberine	10µg /mL	4,7
5	Soyabean, fava beans, and kudzu.	Genistein	Efflux transporter (M - RP) Inhibition.	Oral	Epigalllocatechin-3-gallate Paclitaxel	3.3 mg/kg or 10 mg/kg	4,7
6	Peppermint (*Mentha Piperita*)	Piperine	Local mucosal tissue modulation; thermogenic activity	Oral	B-carotene	15 mg/kg	4,7
7	Citrus fruits and grapefruit	Naringin	CYP3A1/2 enzyme Inhibition And P- glycoprotein modulation in rats	Oral	Verapamil, Diltiazem, Paclitaxel	3.3 mg/kg and 10 mg/kg	4,7
8	Pods *of Moringa oleifera* Lam (Family: *Moringaceae*)	Niaziridin	To enhance absorption, it acts against gram-positive bacteria like Mycobacterium smegmatis and Bacillus subtilis, as well as gram-negative bacteria like E. coli.	Oral	Nalidixic acid Vitamin B12 Rifampicin Ampicillin		4,9
9	Shilajit	Fulvic Acid	Metabolism enhancement (enhanced drug water Solubility)	Oral	Glibenclamide Insulin Pentazocine		6,7
10	Vegetables, citrus fruits, grains, leaves	Quercetin	The efflux transporter is inhibited (P-GP).	Oral	Ranolazine Irinotecan Verapamil Doxorubicin		7
11	Tea leaves, gallnuts, oak bark, sumac, witch hazel.	Gallic Acid Esters	Metabolism and Inhibition of CYP3A	Oral	Nifedipine		7
12	Red vegetables and fruits	Lycopene	Mechanism of LDL- receptor for targeted hepatic delivery	Oral	Simvastatin		7

12	*Heracleum Stenopterum*	Flavonoid-Tamarixetin	Inhibition of metabolism (CYP2C isozyme)	Oral	Fluvastatin		7
14	*Streptomyces olivoreticuli*, bovine lung tissue	Bestatin, Aprotinin	Inhibition of Metabolism	Pulmonary	Granulocyte-colony stimulating factor		7
15	Cod-fish	Extract of cod-liver oil	No known mechanism	Buccal	Ergotamine tartrate		7
16	*Tolypocladium inflatumgams*	Cyclosporine A	P-gp inhibition	Oral	Clopidogrel		7
17	Aloe vera leaf or gel	Aloe vera extract	Intercellular modulation {buccal} and tight junction modulation{oral}	Buccal Oral	Didanosine, Insulin, Atenolol		7,10
18	Turmeric (*Curcuma longa)*	Curcumin	Suppression of the efflux transporter (Pgp); inhibition of the CYP3A4 metabolism	Oral	Midazolam, Mycohenolic acid, Norfloxacin Midazolam, Mycohenolic acid, Norfloxacin	12g/day	7,10
19	PEG (polyethylene glycol) glycerides	Gelucire	Solubilizer	Oral	Silymarin		8
20	Fruit of *Capsicum annum Linn*, Family: Solanaceae	Capsaicin	The absorption of capsicum enhances the AUC of the drugs	Oral	Theophylline		9
21	*Sinomenium acutum*	Sinomenine	Inhibition of P-gp efflux transporter	Oral	Paeoniflorin	90mg/kg	9

6. Classification

6.1. Classification of Bioenhancers on the Basis of Origin

6.1.1. Plant Origin

Piperine, Curcumin, Naringin, Quercetin, Niaziridin, Carum carvi, Capsaicin Cuminum, cyminum, tevia, Lysergol, Glycyrrhizin, Ginger, Allicin, Aloe vera, Simomenin, Genistein, Peppermint oil, Gallic acid, Ellagic acid, Ferulic acid, 5-hydroxyHydnocarpin, Ammannia, multiflora

6.1.2. Animal Origin

Cow Urine Distillate, Capmul

6.2. Classification of Bioenhancers based on Mechanism of Action

6.2.1. Permeation Enhancers

Essential Oils obtained from Cuminum cyminium, Carum carvi, Zingiber officinale

6.2.2. CYP3A4 Inhibitors

Naringin, Quercitin, Gallic Acid Esters-Propyl Gallate

6.2.3. BCRF Inhibitors

Camptothecin

6.2.4. Solubilizers

Cyclodextrins, Fulvic Acid, Gelucire

6.2.5. Miscellaneous

Nitrile Glycosides, Lysergol, Glycyrrhizin, Cow urine distillates

6.2.6. P-GP Inhibitors

Piperine, Sinomenine, Genistein3

7. Detailing of Important Bioenhancers: Fulvic Acid

Fulvic acid is derived from Shilajit, a blackish-brown exudation that contains two kinds of organic compounds: humic substances and non-humic organic metabolites. The molecular weights of humic substances range in many thousands for humic acids, in millions for polymeric humins, and on the scale of hundreds for the fulvic acid component. The low molecular weight molecules found in and around shilajit-bearing rocks are known as non-humic substances and are derived from marine fossils, plants, and microbes. With a porous structure, Fulvic acid possesses voids of diameter around 200 to 1000 Å and a molecular weight ranging between 700 to 2500. By filling the cavities in the pure carrier of fulvic acid with a water-insoluble substance in an estimated amount of approximately 0.5 to 40 % per weight of the fulvic acid carrier, the biological action of a pharmacological, dietary, or aesthetic ingredient could be enhanced. This can be accomplished by physically mixing the medicament and its transporter and chemical

bonding between the two, such as ligand-complex/chelation, reversible covalent bonding, and charge-transfer complexes. When the active substance dissolves in water, it is set free to accomplish its intended function. Fulvic acid boosts drug absorption and bioavailability by increasing the solubility in water of active components.[4,6]

8. Method of Extraction

Fulvic acid was extracted using a slightly modified published approach (Ghosal, 1989). Shilajit, in raw form, was isolated, employing heated organic solvents of rising polarity to eliminate the bioactive components. The residual (marc) was dissolved in 0.1N NaOH with periodic shaking when nitrogen was present. The humic acids were precipitated by filtering the suspension and acidifying the supernatant to a pH of about less than 3. The filtrate was shaken with microporous ion exchange resin and was eluted with aq—solution of 0.1 N NaOH. The Na+ ions were replaced with H+ ions after passing through hydrogen-saturated positive ion exchange resin. To synthesize the amorphous Fulvic acids, the obtained solution of fulvic acid was first concentrated and then dried using a freeze dryer. [6] To gain a better knowledge of the complex formation behavior of furosemide, fulvic acid isolated from the bioactive substance shilajit was studied. Due to the limited aqueous solubility at the gastrointestinal pH, Furosemide (FSM) is a weakly soluble drug with less bioavailability by oral route. Fulvic acid's impact on FSM's aqueous solubility, dissolution rate, and permeation was investigated. Complexation with Fulvic acid was tried to enhance the miscibility of FSM. Grinding, solvent vaporization and Lyophilization processes were used to create complexes in the mole ratios (FSM-FA) of 1:1 and 1:2. Fourier Transform Infrared Spectroscopy, Differential scanning calorimetry, X-Ray Diffraction, and Scanning Electron Microscope spectrum investigations were utilized to recognize the compounds. The release and solubility of FSM from the 1:2 freeze-dried complex improved dramatically compared to other complexes. The optimized complex (1:2 freeze-dried FSM-FA) had significantly higher permeability across the gut sac in 1 hr than FSM alone. When FSM was coupled with Fulvic acid, significant improvements in bioavailability properties such as drug dissolution, solubility, and permeability were reported. Thus, FA can be employed in the industry to design and optimize FSM dosage formulations. [6]

Another research concluded that when Glibenclamide, an oral hypoglycemic drug that is only slightly miscible in water, is coupled with pure fulvic acid, it becomes entirely miscible in water and possesses a greater hypoglycaemic effect. [4] Also, Pentazocine is a narcotic analgesic with a broad first-pass action and a 30 to 35 % oral bioavailability. When taken orally, Pentazocine-Fulvic acid in the dosage of 5 mg+50 mg combinations exhibited a strong analgesic effect that began within 30 min and persisted for 180 min. [4]

9. Gelucire

Gelucires are Polyethylene glycol esters made up of monoglycerides, diglycerides, and triglycerides, including diesters and monoesters of polyethylene glycol. They are inert semisolid waxy amphiphilic excipients with surface-active qualities that form a thin dispersion or emulsion when they come into contact with water, resulting in immediate-release solid dosage forms which are not soluble in water. The creation of a semisolid dispersion system with Gelucire 44/14 was employed in the past in research to boost the oral bioavailability of silymarin, a herbal hepato-protectant. The solvent–fusion approach was utilized to make binary systems, after which DSC validated them. The dissolution rate of silymarin semisolid dispersion was revealed to be increased (1.5 to 7.0 folds that of pure silymarin at 1 % to 15 % Gelucire 44/14 concentrations), which boosted the dissolving rate of the silymarin- Gelucire combination (91 % within 10 min). [8]

10. Naringin

The pericarp of citrus fruits, including grapefruits, naturally contains naringin, a flavanone glycoside (Citrus paradisi; Family: Rutaceae). Naringin can block the efflux pump of cytochrome P450, specifically CYP3A4 and P-Glycoprotein. According to a literature review, naringin possesses antiviral, anticancer, hepatoprotective, antioxidant, anti-inflammatory, and antiulcer properties. Naringin inhibits the action of the CYP3A4 enzyme in the microsomes of the liver and enhances ascorbic acid-induced lipid peroxidation. Naringin has a potent inhibitory effect against acyl CoA-cholesterol-O-acyltransferase, macrophage-lipid complex aggregation inhibition, and hepatic disease prevention or treatment activity. Pre-treatment with naringin appears to modify the pharmacokinetics of drugs like tamoxifen, verapamil, diltiazem, and paclitaxel that are P-GP and/or CYP3A substrates in rats/rabbits overdosage of 3-30 mg/kg in past research. According to a research paper aiming at analyzing the effect of naringin on the antihyperlipidemic activity of Atorvastatin (AST) in tyloxapol-induced hyperlipidemia in Wistar rats, the observed activity was associated with blood levels of AST in experimental animals. In comparison with animals that were given AST alone at doses of 25 and 50 mg/kg, animals given AST combined with naringin in two doses 15 mg/kg and 30mg/kg) showed higher percent reductions in both cholesterol and triglycerides, revealing that the significantly higher percent reduction in cholesterol and triglycerides was proportional to the increase in the concentration of AST in the blood plasma. The results show that administering naringin along with AST increased the amount of AST in the blood plasma. The findings of this study showed that naringin can be used as a natural

bioavailability enhancer. Assisting patients with AST and Naringin may improve the therapeutic efficacy of AST. [4,11] In another similar study, a single dose of AST was used to test its bioavailability in rats. Design-Expert® software was used to tweak the technique's process, formulation, and concentration parameters. According to the findings, pre-treatment with 2 mg/kg naringin for 15 min enhanced AST bioavailability by about nine-fold. [12]

11. Esters of Gallic Acid

Gallic acid is a water-soluble phenolic acid obtained from grapes and the leaf of many plants, including gallnuts, tea leaves, and oak bark and is also a gallotannin, a broader group of polyphenols of plants. Hydrolysis transforms gallotannins into the free form of gallic acid inside the GI tract. It is said to be having several health advantages, including anticancer, anti-inflammatory, cardioprotective, and anti-diabetic qualities, as per the research. Gallic acid inhibits the P-Glycoprotein-mediated drug efflux and CYP450-related isozymes, including CYP3A4. [13] Both in vitro and in situ transport assays were performed to look into the impact of gallic acid on the transfer of diltiazem. In vitro, research was carried out using gut sacs (non-everted) from the intestinal tissue of the Wistar rat. When compared with that of the control group, it is found that the relative diltiazem permeability increased by 4.4, 5.1, and 4.9 times in the parts where gallic acid was present in the non-everted intestinal gut sacs. [13] For the purpose of performing the intestinal perfusion in situ single-pass research, rats were categorized into 4 groups (n = 5): control, standard inhibitor, and pre-treatment with either gallic acid or ellagic acid. The cannulated section of the intestine was perfused with a phosphate type of buffer of saline pH around 7.2 containing phenol red about 50 mg/ml, and the concentration of diltiazem was 100 g/ml. A steady flow rate of 0.2 mL/min was preserved for 90 min, with samples collected every 10 min. According to the outcomes of the in-situ experiment, prior treatment of gallic acid (concentration-50 mg/kg) for about 7 days resulted in a substantial (p 0.05) increase in the diltiazem transport in Wistar rats as compared to the control group (diltiazem alone). Diltiazem's Cmax, AUC0–t, and AUC0– were all elevated by 1.90, 2.06, and 2.08 times, respectively.[14] According to these results, it is found that gallic acid inhibits both P-glycoprotein and CYP3A4, which results in a large increase in diltiazem's bioavailability. [13] In a comparable in situ single-pass intestinal perfusion research in the Wistar rats, the transport of the drug- metoprolol was examined to decide the pharmacokinetic properties of orally administered metoprolol. The Wistar rats were given a 7-day pre-treatment with 50 mg/kg gallic acid prior to the investigation. The Area Under the Curve and Cmax values of metoprolol both increased significantly. Gallic acid was revealed to be increasing bioavailability (oral) by reducing the activity of CYP2D6 in the liver, resulting in reduced metoprolol metabolism. [14]

12. Cumin

It is acquired from the herb Cuminum cyminum. The essential oil from cumin is helpful as a natural bioenhancer. Cuminum cyminum is a small, thin annual herb widely grown around the Mediterranean coast in South-East Europe and North Africa. Family- Apiaceae. 15 3,5-dihydroxyflavone-7-O-β-D galactouronide4-β-O-Dglucopyranoside is the bioenhancer content present in the cumin. [16]

The bioavailability/bioefficacy enhancing activity was attributed to a few volatile oils, luteolin, and flavonoids. Luteolin is a potent inhibitor of P-glycoprotein. 15 Cumin contains other volatile components and essential oils such as Cuminaldehyde, cymene, and terpenoids. Cumin inhibits p-gp efflux pump. [1]

P- glycoprotein efflux pump is an efflux membrane transporter, which limits the entry of different drugs and toxic substances into the cell. Thus inhibition of the p-GP efflux pump by cumin leads to a rise in the drug concentration in serum. In other words, cumin enhances the permeability of a hydrophobic pharmaceutical drug that is orally administered, thereby increasing its bioavailability. [4] The chemical constituents were extracted from the cumin seeds by the following process- Drying of the cumin seeds done in an oven at 60 oC until they reached a consistent weight. The seeds were ground into a fine powder and boiled in distilled/deionized water for 72 hr in a water bath at 70 oC. The collected extract was filtered and undergoes freeze-drying using filter paper (542, pore size 2.7 m). [17] The potent dose of bioenhancer extract of cumin ranges from 0.5-25 mg/kg of body weight. [1] Cuminum cyminium is useful as a bioenhancer to reduce microbial resistance to anti-infective drugs like antifungal and antibiotic agents. Cumin potentiates the activity of anti-infective drugs. This property could be useful in reducing bacterial and yeast resistance to anti-infective drugs. Due to bioenhancer, lower doses of anti-infective drugs are required to inhibit growth or kill pathogens and other harmful microorganisms.[4] Sachin et al. Examined the effects of 3,5-dihydroxyflavone-7-O-β-Dgalactouronide-4-β-O-D-glucopyranoside on rifampicin levels in the plasma of rats. Cumin extract enhances the levels of rifampicin in the plasma of rats. The Cmax of rifampicin was increased by 35 %, while the AUC was enhanced by 53 %. 1,16 Cumin also has carminative, estrogenic, anti-inflammatory, and antioxidant activity. [16] Curcumin is accepted worldwide as a nutraceutical that improves people's general health. [18]

13. Ginger

Ginger is obtained from the dried, subterranean rhizome or stem of the plant Zingiber officinale belonging to the family Zingiberaceae. The ginger plant is herbaceous. [4] The active ingredients in ginger oleoresin (called Gingerin) are - Gingerols, Zingerones, and Shogaols. It also contains resins, phenols, and other chemicals. [4] The pungent characteristic

of ginger is due to gingerol. [19] Rhizome of ginger also contains volatile oil (up to 1 to 3 %). This volatile oil content causes the characteristic odor of ginger. [19] The volatile oil contains sesquiterpene hydrocarbons (up to 50 %), sesquiterpene alcohols, monoterpenoids, etc. [4] Ginger has a strong action on the mucous membrane of the gastrointestinal tract. [19] By regulating GI tract function, gingerol aids in improved drug absorption through the GI tract. [16] The bioavailability-enhancing effects of ginger range from 30 to 75 % when administered alone. [19]

- The extraction of volatile oil from zingiber Officinale is done by using steam distillation. The pale yellow, viscid oil produced by steam distillation of dried, cracked, and comminuted ginger is 1-3 %.[20]
- The dried powder of zingiber officinale is extracted with a suitable solvent to obtain ginger oleoresin. The solvents used are alcohol or acetone. [20]

The bioenhancer extract of ginger has an effective dose varying from 10- 30 mg/kg body weight. [16]

The extract is useful in amounts ranging from 2.0 to 250 mg. [4] Ginger is one of the most extensively used spices in India. [4] It acts as a carminative and stimulant to the GIT. It is very popular as a home treatment for bloating and colic. Topically, it is beneficial as a local stimulant and rubefacient. [4] Ginger also possesses antimicrobial, antifungal, antiulcer, and antithrombotic activities. [19]

Table 2. The percentage increase in the bioavailability of different drugs by cumin.[16]

Drug	Category	Enhancement in Bioavailability (%)
Rifampicin	Antibiotic	250
Cycloserine	Antibiotic	89
Ethionamide	Anti-tubercular	78
Cefadroxil	Antibiotic	90
Cloxacillin	Antibiotic	94
Fluconazole	Antifungal	170
Zidovudine	Antiviral	330
5-fluorouracil	Anticancer	335

Table 3. Enhancement in Bioavailability of Drugs from ginger when given alone

Drug	Category	Enhancement of bioavailability (%)
Rifampicin	Antibiotic	65
Ethionamide	Antitubercular	56
Azithromycin	Antibiotic	78
Ketoconazole	Antifungal	125
Zidovudine	Antiviral	105
5-fluorouracil	Anticancer	110
Cisplatin	Anticancer	56
Alprazolam	CNS drug	76

Table 4. Increase in the bioavailability of different drugs after dosing of caraway

Drug	Category	Enhancement in bioavailability (%)
Rifampicin	Antibiotic	110
Cycloserine	Antibiotic	75
Ethionamide	Antitubercular	68
Amphotericin-B	Antifungal	78
Zidovudine	Antiviral	92
5-fluorouracil	Anticancer	90

14. Caraway

Caraway consists of the ripe, dried fruits of Carum carvi, which belong to the family Umbelliferae. [16] Fruit of the caraway contains essential oil (3 to 7%), fatty acids (10 to 18%) (petroselinic, linoleic, and oleic acids), protein (20 %), carbohydrates (15 %), phenolic acid, flavonoids. Tannins, alkaloids, and terpenoids are also available caraway.[21] Flavonoids present in caraway fruit are quercetin and kaempferol.[21] Carvone and limonene are the main constituents present in caraway oil.[22] Caraway inhibits the P-gp transporter. 1,21 It improves drug absorption through the gastrointestinal tract. It enhances the permeability of the main constituent of a drug inside the microorganism/ pathogens, e.g. Tuberculosis, thereby potentiating the activity of the drug. Caraway decreases the metabolism rate of the drugs through the liver and intestines. [4] The bio-enhancing effect of caraway could be attributed to increased mucosal or serosal penetration. [22] Caraway is either given alone or given in combination with ginger and piperine. The active dose of the bioenhancer ranges from 5 to 100 mg/kg of body weight. (caraway-1 to 50 mg/kg, ginger – 1 to 150mg/ kg of body weight and piperine 3-15 mg/kg body weight. [4] Caraway is widely utilized as a spice and carminative in food products and pharmaceutical industries. [21] Caraway is also used as a stomachic, aromatic, and diuretic.[1] Caraway also possesses antimicrobial, Anti-diabetic, and anti-inflammatory activity.[21]

The administration of caraway is not recommended for patients with liver diseases or any other biliary disorder. [21] It is not a good idea to use caraway oil during pregnancy and lactation. Caraway has no side effects on human beings. Acute toxicity may occur if caraway oil and caraway aqueous extract dose exceeds 400 mg/kg and 3200 mg/kg of body weight. [21]

15. Piperine

Piperine is the main alkaloid found in Pepper fruits belonging to the Piperaceae family, and it has various medicinal properties. Brandy flavoring is made from black pepper fruits. Moreover, as a pickle preservative in various dishes, beverages, desserts, and scents, It has the title of "King of Spices." The black-coloured pepper fruit alone accounts for about 35 % of global spice production. [23,24]

Production bioenhancers are thought to improve oral health. By inhibiting the drug's bioavailability, companion drugs can be made less effective. Either altering the permeability of the intestinal mucosa via the metabolizing enzyme cytochrome p450 or by changing the permeability of the intestinal mucosa via the TER (transepithelial electrical resistance factor) is a measure of the electrical resistance of the epithelial cells. [25,26] During this process, the pore size between the mucosal epithelial cells is expanded, increasing the permeability of the intestinal mucosa and allowing for quicker absorption. Piperine operates by either increasing gastrointestinal osmosis or decreasing gastrointestinal osmosis by preventing the decomposition of companion medication in the liver.

16. Sinomenine

Sinomenine is an alkaloid derived from Sinomenium acutum frequently used in China and Japan to treat rheumatic and arthritic disorders. Through gastric gavage, male Sprague-Dawley rats weighing 250 to 300 g were given a single dose of paeoniflorin (150 mg/kg) and sinomenine hydrochloride (90 mg/kg). A blood sample was obtained from a jugular vein before and after each treatment for 10 min to 12 hr. An HPLC test was used to determine paeoniflorin plasma concentrations. After manipulating sinomenine, the levels of paeoniflorin were increased, delayed, and increased, while MRT was extended, decreased, and reduced. In rats, sinomenine hydrochloride significantly improved paeoniflorin oral bioavailability.[27] Sinomenine at doses of 16 M and 136 M increased paeoniflorin (20 M) osmosis by 1.5 and 2.5 times, respectively, and improved paeoniflorin bioavailability in rats. [27]

17. Genistein

Genistein is an anticancer and anti-inflammatory isoflavone present in several food plants, including soybean (Glycine Max) and kudzu (Pueraria lobata).[28] It belongs to the isoflavone class of flavonoids. It inhibits the efflux pumps P-GP and BCRP. After oral administration of paclitaxel at a dose of 30 mg/kg, the presence of genistein (10 mg/kg) induces a 54.7 % rise in area under the curve (AUC) and a 35.2 % decrease in total plasma clearance.16 It is a phytoestrogen with a lot of uses. [29]

18. Lysergol

Lysergol, a Phyto molecule derived from the Morning Glory Plant (Ipomoea spp.), is a good herbal bioenhancer that boosts the killing power of several antibiotics. It has been discovered in higher plants such as Riveacorymbosa, Ipomoea violacea, and Ipomoea muricata. The bio-enhancer characteristics of lysergol are being studied. The dosage level of lysergol is 1 to 10 g/mL. However, 10 g/ml is preferred as a bioenhancer and bioavailability bioenhancer. Antibiotics, including rifampicin, doxycycline, and ampicillin, have better oral bioavailability. Lysergol boosts an antibiotic's antibacterial activity by 2 to 12 times. It kills E. Coli (ATCC 10536), B. Subtilis (ATCC 6051), M. smegmatis (ATCC 14468), and other Gram-positive and Gram-negative bacteria.[30] Patil et al. [31] discovered that lysergol increased berberine bioavailability after oral dosing in Sprague-Dawley rats. Using lysergol (10 g/ml) in combination with rifampicin to boost antibiotic action against a variety of bacteria. [31]

19. Cow Urine Distillate

Cow urine distillate is more effective than cow urine in increasing the success of antibacterial, antifungal, and anticancer drugs.[32] Cow urine can be used as a zinc bioenhancer and has antitoxic properties when it comes to cadmium chloride toxicity. Male adult mice exposed to cadmium chloride had a reproductive rate of 0 %. Cadmium chloride in cow urine distillate with zinc sulfate-treated animals, on the other hand, had a 90% reproductive rate, 100% bioavailability, and 90% survival rate. In addition to low urine can be used as a zinc bioenhancer and has antitoxic properties when it comes to cadmium chloride toxicity. Male adult mice exposed to cadmium chloride had a reproductive rate of zero percent. Cadmium chloride in cow urine distillate with zinc sulfate-treated animals, on the other hand, had a 90% reproductive rate, 100% bioavailability, and 90% survival rate. In addition to lactation indices, the fertility index in the cadmium chloride group was [15]. Cow urine distillate was also found to have an 88% content. Cow urine distillate is a natural remedy to cadmium chloride poisoning and can be used as a zinc bio enhancer as a result of these studies. [33] The activity of rifampicin against Escherichia coli was increased by 5 to 7 times in the presence of cow urine distillate and 3 to 11 times in the presence of gram-positive bacteria. It most likely works by allowing antibiotics to pass through the membrane of the gastrointestinal system more easily. Transit usage has increased by 2 to 7 times. [33] Cow urine distillate increased the effect of gonadotropin-releasing hormone conjugate on female mice's reproductive hormones and the estrous cycle. [34] In male mice, cow urine distillate significantly improved the effect of gonadotropin-releasing hormone.

20. Nitrile Glycoside

Moringaoleifera plant pods were used to create Niaziridin, a new nitrile glycoside. The biomolecule enhances the bioavailability of medications, vitamins, and nutrients by improving their oral absorption via the gastrointestinal barrier. As a result, niaziridin can be used in combination with other drugs and nutrients to reduce drug-related toxicity, as well as chemotherapy expense and duration. Niaziridin is most effective when used in quantities of 0.1 to 10 g/mL. The bioactive fraction increases the efficacy of antibacterial, antifungal, and anti-

tuberculosis medication by 2 to 80 times. The effectiveness of rifampicin, ampicillin, and nalidixic acid against gram-positive bacteria, for example, was increased by 1.2 to 19 times. It increased the effectiveness of azole antifungal medications like clotrimazole against Candida albicans by 5 to 6 times. It also improves the absorption of vitamin B12. [4,7] Liquorice' bio-enhancing actions are due to glycyrrhizin, a non-alkaloid substance present in the root.

21. Glycyrrhizin

Antibiotics and other medications have better oral bioavailability, including anti-infective and anticancer therapies. The compound improves the absorption/uptake of antibiotics and other substances across the cell membrane in plant and animal cells and Gram-positive and Gram-negative bacteria. It has no antibacterial or cytotoxic properties of its own, making it a safe candidate for lowering drug dosage in anti-infective and anticancer treatments to avoid drug resistance and side effects. Bio-enhancing concentrations of glycyrrhizin range from 0.05 to 50% of the weight of antibacterial compounds, 0.1 to10 % of the weight of nutraceutical compounds, and 0.25 to 20% of the weight of antifungal agents.18It boost the anticancer drug taxol (paclitaxel cell's) division inhibitory activity against the MCF- 7 breast cancer cell line growth and multiplication by 5 times. Antibiotics like rifampicin have also been discovered to aid antibiotics like tetracycline, nalidixic acid, ampicillin, and vitamins B1and B12 get around tetracycline, nalidixic acid, ampicillin and vitamins B1 and B12 go through the gut barrier by a factor of 2- 6.[4,7] According to a study, the extractor substance produced by Glycyrrhiza glabra used as a bioenhancer and facilitator of nutritional chemicals, medications, and molecules selected from anti-infective and anticancer substances.

22. Capmul

Capmul MCM C10 is a glyceryl monocaprate derived from edible fats and oils and extensively utilized in lip cosmetics. It is one of the most widely used bioenhancers. According to a trial carried out on rats, the antibiotic ceftriaxone enhanced the bioavailability of ceftriaxone by 80% when given together with capmul.[35]

23. Gokhru

Tribulus Terrestris Linn (Zygophyllaceae) is the source of gokhru extract, a widely cultivated extract used in Ayurvedic medicine. Carboline alkaloids, Saponins, flavonoids, and steroids are among the Phytochemicals previously found in T. Terrestris. Gokhru extract has been utilized as a diuretic, anti-inflammatory, anabolic, spasmolytic, muscle relaxant, hypotensive, and hypoglycemic medication in the past, but it has also been shown to affect the bioavailability of co-administered pharmaceuticals. [7] In an investigation, Metformin HCl tablets (175 to 500 mg) were prepared with varying quantities of Gokhru extract (0 to 100 mg) and then tested using a chicken intestinal everted sac model. The drug absorption improvement capabilities of Gokhru extract were confirmed in this investigation, with improved metformin penetration through chicken intestinal membranes increasing from 29% to 54%. 36 In another study, a methanol extract was made from dried T. Terrestris leaves and applied to the mucosal side of goat intestinal tissues using an everted sac method, along with salicylic acid (aspirin). The Gokhru extract improved aspirin transport, and it was suggested that the saponins actions on the membranes were responsible for the increased permeability. [37]

24. Aloe Vera Gel

Using Franz diffusion cells, the effect of Aloe vera gel on the permeability of didanosine (ddi) across porcine buccal mucosae was examined. The control solution included ddi alone (5, 10, 15, 20 mg/mL) in PBS (phosphate buffer saline) at pH 7.4, while the test solution had ddi (20 mg/ml) in the presence of Aloe vera gel (0.25, 0.5, 1, 2, 4, and 6 % w/v).

Table 5. Bioenhancer formulations in the market

Sr No.	Formulation	Active therapeutic ingredient	Biological activity	Use
1	Greentea-lipid-based systems	Ginsenoside	Anticancer, antioxidant, and nutraceutical.	Increases absorption
2	Capsaicin Transferosomes	Capsaicin	Analgesic	Increase skin penetration
3	Colchicine Transferosomes	Colchicine	Anti-gout	Increase skin penetration.
4	Rutin-alginate chitosan microspheres	Rutin	Cerebrovascular and Cardiovascular action	The cardiovascular and cerebrovascular systems are being targeted for treatment.
5	Liposome encapsulated silymarin	Silymarin	Hepatoprotective	Enhances bioavailability

Aloe vera gel considerably increased the buccal permeability of ddi at doses of 0.25 to 2% w/v, with enhancement ratios ranging from 5.09 (0.25 % w/v) to 11.78 (2 % w/v). Increased ddi permeability across the buccal region was reported at higher Aloe vera gel concentrations (4 and 6 % w/v). [7,38] Formulation of Bioenhancers in the Market 9 Table No. 5: Bioenhancer formulations in the market.

25. Discussion

This review article is an attempt to learn about bioenhancers, which are a popular method for improving the bioavailability of poorly bioavailable medications. To begin, we investigated and discussed bioavailability and the factors contributing to poor medication bioavailability. Secondly, we focused on bioenhancers, including their history, mode of action, numerous characteristics and classifications, as well as a detailed discussion of a few important bioenhancers.

26. Future Perspective

Many scientists and pharmaceutical corporations are working to improve the bioavailability of a large number of powerful drugs that are now ineffective. Natural bioavailability enhancers provide a fresh method for decreasing pharmaceutical doses and making treatment more feasible and accessible to a broader population. Natural bioenhancers also aid in preventing drug resistance in microbes, which is a major issue for humanity. [22] As new chemicals have been produced, pharmaceutical research has had a lot of success. However, the newly discovered compounds have several drawbacks, including low water solubility and bioavailability, which necessitate the use of bioenhancers. The pharmacokinetic and pharmacodynamic features of these poorly accessible medicines can be altered by combining them with bioenhancers. [6,22] Piperine remains the only endogenous bioenhancer that has been extensively researched in pharmacological classes such as antihyperglycemics, antimicrobials, analgesics, anti-HIV, antiepileptics, antihyperglycemics, chemotherapeutics, cardiovascular therapies, and immunosuppressants. [22] Many natural bioenhancers are still unexplored and need to be researched in a few key areas. There is a myriad of unknown plants with bio-enhancing capabilities that need to be researched. [6] Naringin, a flavone glycoside produced from grapefruit juice, has been recognized as a significant bioenhancer of anticancer, CVS, and steroidal pharmaceuticals. However, it has yet to be studied in sectors like anti-inflammatory, HIV, and CNS therapies. Similarly, genistein, sinomenine, and niaziridin have not been well investigated in a wide range of drugs. Research must be comprehensively performed to see if these bioenhancers can be used to improve bioavailability via different routes of drug administration. Since numerous neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease, and others have become extensively pervasive, there is a high demand for medications that can directly operate on the CNS as medications need to penetrate the blood-brain barrier to act on the CNS. These natural bioenhancers are being used in novel drug delivery systems such as nanoparticles, ethosomes, liposomes, microspheres, and transferosomes to target poorly bioavailable medications to their particular areas of the body, especially the brain, due to technological advances. [6, 22]

27. Conclusion

The expense of treatment has been a major issue in developing countries such as India, Pakistan, Nepal, and Indonesia. 16 This is due to the fact that many of the critical medications required today are poorly bioavailable, making them subtherapeutic. As a result, increasing the bioavailability of such medications is critical. Based on the findings of this Review, we can infer that using Bio-enhancers is one of the most important approaches for increasing the bioavailability of poorly bioavailable medications. Bioenhancers is a novel and innovative concept based on Indian medicine's historical and traditional framework. As a result, treatment costs, toxicity, and side effects are reduced. Furthermore, they are easy to make and obtain, are cost-effective, safe, non-addictive, and efficacious, and have a wide range of applications. Natural bioenhancers positively impact a country's economy by lowering the drug's dose. It lowers the risk of toxicity associated with overdosing on medication with low bioavailability. [22] Because the bulk of bioenhancers come from herbal sources, they play an important role in innovative medicine development approaches regarding cost. [16] As a result, more comprehensive and in-depth research on various classes of bioactives for their bioavailability-enhancing capability should be conducted so that better pharmaceutical formulations can be introduced to the market, as these bioenhancers open up new opportunities in the pharmaceutical and healthcare industries. [4]

27.1. Abbreviation

AUC: Area under Curve; GIT: Gastrointestinal Tract; P-gp: P Glycoprotein; TER: Transepithelial Electrical Resistance, HPLC: High-Performance Liquid Chromatography; MRT: Mean Residence Time; ATCC: American Type Culture

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