Review Article

An Indication of Herbal Bioenhancers: Biological Importance and Bio-Potentiation of Drugs

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ABSTRACT

In modern medicine, "Bioenhancers" are an innovative concept that is utilized to increase the effectiveness of drugs. The most important factor in determining how effectively a medication will carry out its therapeutic function is its bioavailability. Although the idea has been studied and tried in a variety of modern treatments, its roots are often found in the ancient system of medicine (Ayurveda). Herbal bio-enhancers perform exceptionally well in terms of security, efficacy, and accessibility. Herbal bio-enhancers are widely used to increase the bioavailability of antibiotics, nutraceuticals, anticancer, antitubercular, and cardiovascular medications in order to accelerate the onset of action. Modern applications use herbal enhancers to increase a medicine's bioavailability by numerous innovative drug delivery methods, including liposomes, transferases, ethosomes, nanoparticles, etc. by different routes of administration. In modern medicines, many compounds, like piperine and quercetin, are formulated into contemporary pharmaceuticals having a scientific purpose. An example of this is the combination of rifampicin, isoniazid, and piperine used in anti-tubercular treatment. Systemic approaches that can connect traditional approaches with new principles are the most likely means of achieving a breakthrough since their appropriate conjunction with other pharmaceuticals lowers the price of expensive drugs.

Keywords: Herbal Bioenhancers, Bioavailability, Drugs, Bio efficacy, Synergism.

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INTRODUCTION

Modern methods are being used to discover new substances with diverse mechanisms of action, while also considering the economic feasibility of drug development, resulting in lower medication costs. There is a strong emphasis on studying parameters like bioavailability to increase treatment effectiveness while reducing costs.[1]. Bose first saw the rise in the antiasthmatic effects in 1929, when he first reported a long pepper by adding vasaka (Adhatoda vasica) leaves to its. In 1979, C. K. Atal, a different scientist who works at the Regional Research Laboratory in Jammu (Indian Institute of Integrative Medicines), scientifically assessed piperine as the first bioenhancer. [2] Since ginger (*Zingiber officinale*), black paper (Piper nigrum), and long paper (Piper longum) are all often utilized, Mr. Atal made the claim that Trikatu boosts the effectiveness. [3] When he examined all of the constituents, he discovered that piperine, an active chemical in Piper longum, enhances the bioavailability of many medications. As a result of this research to boost bioavailability, the word "bioenhancer" was created.[4]

Fundamentals of Bioenhancers

Bioenhancers are natural products without their own usual therapeutic effect when used at the dose. It improves the bioavailability and bioefficacy of the targeted medicine when coupled with it, which potentiates the drug's pharmacologic action. In Ayurveda, the concept of a bioenhancer is known as Yogvahi. Regarding Yogvahi, there are two ideas,

1 Anupaan: Yogvahi is consumed together with meals in order to improve its impact. Example: Amritdhara drops used to treat digestive disorders; increased potency by adding drops to sugar.

2. Sehpaan refers to a machine used in the manufacture of pharmaceuticals. Example: Brahmi ghrita.[5]

Bioavailability is an important parameter that governs drug action. Drugs with better bioavailability can provide efficient therapeutic action with a minimum dose, which can decrease the hepatic and nephrotic load as there is a decrease in the amount of dose required for therapeutic action. The factors that majorly affect bioavailability are solubility, permeability, and first-pass metabolism.[6]Herbal bio-enhancers efficiently increase the absorption of drugs without a significant alteration and interference in the physiology of the body and the action of the drug. [7] In the current scenario, herbal enhancers are used to improve the bioavailability of various drug activities used to treat the diseases associated with the central nervous system (CNS), gastrointestinal tract, and cardiovascular system (CVS).[8] Overall, bioavailability enhancement is an important area of research that has the potential to improve the efficacy and safety of drugs and

nutraceuticals, and herbal bio-enhancers provide a promising approach to achieving this goal.[9]

Advantages /Benefits

The following benefits of bio-enhancers for developing medications

1. The medicine is more effective because of an enhancement of bio-enhancers in bioavailability.

2. Bioenhancers minimize medicine resistance.

3. Eliminates undesirable medication responses and side effects.

4. Decrease total treatment cost.

5. increases a drug's efficiency.[10]

Methods Of Enhancing Bioavailability:

To improve the intestinal absorption of inadequately absorbed medications, a variety of strategies have been used. [11]

The Methods of Bio-enhancers are shown in Fig.1.

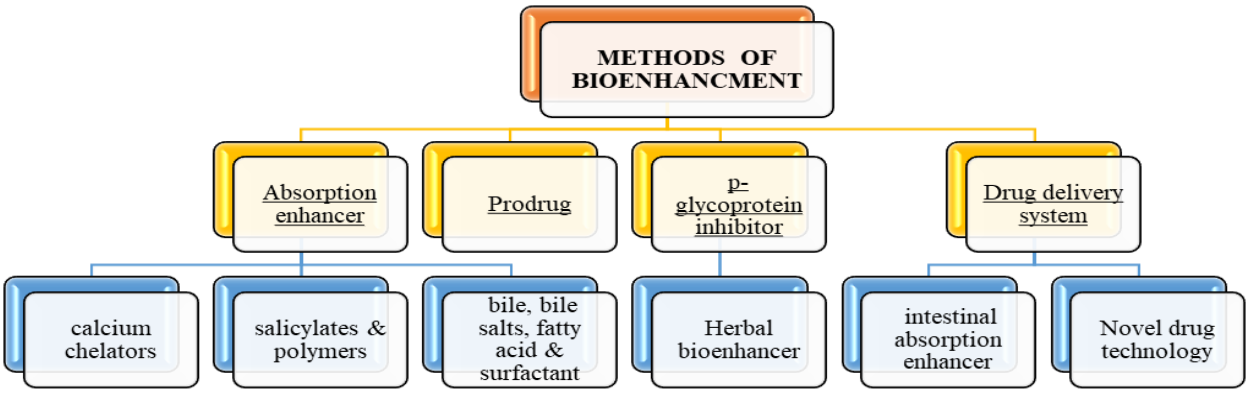

Figure 1: Methods of Bio-enhancement

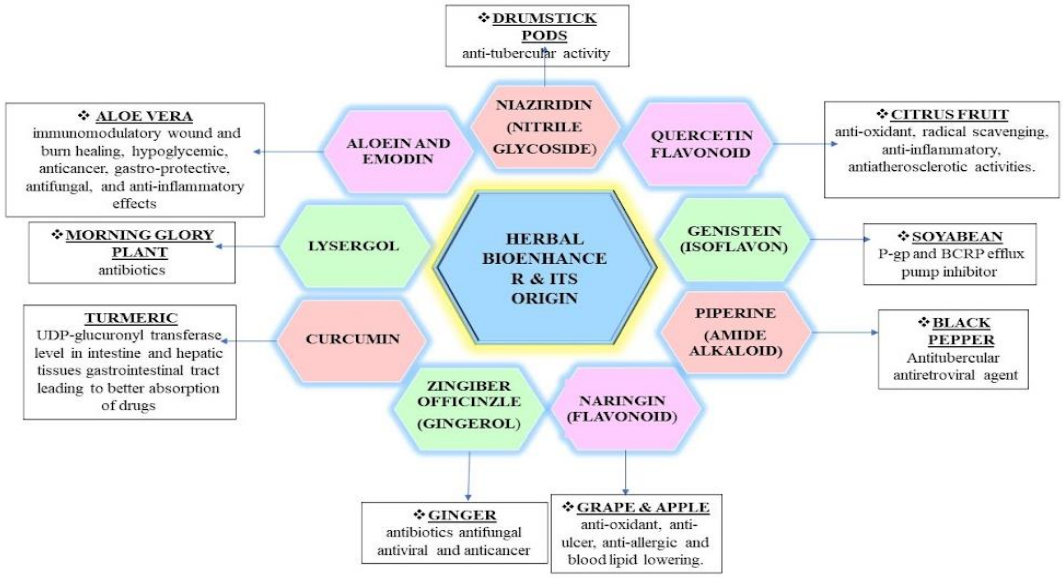

Figure 2: Herbal Bioenhancers and its Origin

Mechanisms Of Action:

Herbal bio-enhancers work in a variety of ways to increase the bioavailability of the medicinal molecule.[12]

1. By enhancing the blood flow, which improves the GIT's ability to absorb medications taken orally.

2. Intestinal motility, gastric emptying time, and gastrointestinal transit inhibition.

3. Extending the time a drug remains in the body by slowing down the excretion process.

4. Decrease in the production of hydrochloric acid and an increase in gastrointestinal blood flow.

5. Glomerular filtration, active tubular secretion through inhibiting P-gp, and passive tubular resorption are all affected, which inhibits renal clearance.

6. Inhibiting the drug's metabolizing enzyme in the liver, intestines, lungs, and several other organs, such as CYP3A4, CYP1A1, CYP1B2, and CYP2E1.

7. By preventing the p-glycoproteins efflux pathway, modifying the signaling process

8. The cholagogues effect.

9. Thermogenic and bioenergetic properties.

10. Suppression of first-pass metabolism, inhibition of the drug metabolizing enzyme, and promotion of the activity of the enzyme gamma-glutamyl transpeptidase (GGT), which improves amino acid absorption.

Classification of Bioenhancers:

On the basis of Origin:[13] (Figure 2)

NATURAL PRODUCTS USED AS BIOAVAILABILITY ENHANCERS

Quercetin

Quercetin, also known as 3,3,4,5,7-pentahydroxyflavone, derives its scientific name from the Latin word quercetin, which means oak forest.[14] Plant pigment quercetin, an effective antioxidant and more specifically a flavonol, is mainly found in onions, grapes, berries, cherries, broccoli, and citrus fruits. It is a versatile antioxidant with the ability to prevent tissue damage brought on by a variety of drug toxicity.[15] The effect of quercetin on the myocardial potency of curcumin against ischemia reperfusion-induced myocardial toxicity. Combination of Quercetin with Curcumin against ischemia-reperfusion injury (IRI) by inducing myocardial toxicity in rats via oral route and concluded an increase in bioavailability and half-life, as well decrease in clearance.[16] The absorptivity of berberine chloride and quercetin on goat intestine by means of Franz diffusion cell, Improves the ex vivo permeability of berberine chloride.[17] The pharmacokinetics of quercetin on losartan and its metabolite EXP3174 in rats improved the C_{max} and the AUC of losartan also reduced C_{max} of EXP3174. later showed herb-drug interaction between quercetin and losartan by preventing the activity of P-gp and the activity of the CYP450 enzyme. [18] The effects of quercetin on the pharmacokinetics of cefprozil and checked the safety of the combination of cefprozil and quercetin also measured mean serum concentrations of cefprozil in the presence/absence of quercetin which exhibited no substantial effects on the pharmacokinetics of cefprozil. [19]

Gentamycin and quercetin increased lipid peroxidation and investigated how gentamicin could cause oxidative stress in human leukocytes and the whole blood of Wistar rats and found that quercetin may have a protective effect on this oxidative stress without changing how effective gentamicin was at killing E. coli and S. aureus strains of bacteria. The effect of acute and short-term intake of high-dose quercetin on CYP3A-mediated metabolism, and concluded that a single dose of quercetin was not toxic when coadministered with midazolam, whereas repeated quercetin intake can reduce systemic exposure to the orally given drug by increasing its CYP3A-catalyzed metabolism.[21]

A combination of both Glimepiride and quercetin increased C_{max}, AUC0-n, AUC total, $t_{1/2}$, MRT, and decreased clearance. Pharmacodynamically suggested that quercetin and glimepiride work better together to reduce glucose levels in diabetic rats.[22]

Quercetin improved the bioavailability of ranolazine in rats. The function of P-glycoprotein (P-gp) in vitro models measures the concentration of ranolazine in the plasma after collecting blood samples at predetermined intervals which leads Quercetin to increase the peak concentration (C_{max}) and AUC of ranolazine Because quercetin inhibits CYP3A4 and P-gp, less ranolazine was transported from the mucosal to the serosal side.[23]

Oral doses of clopidogrel with or without the P-gp inhibitors quercetin telmisartan and cyclosporine led to an increase in the peak plasma concentration of clopidogrel carboxylic acid and the area under the curve for these drugs in rats.[24]

Epigallocatechin gallate (EGCG), is an anticancer constituent in green tea but has poor bioavailability in rats and humans due to its metabolism and its efflux system. So calculated and compare the pharmacokinetic parameters of EGCG alone and with Quercetin/red onions and determined plasma concentrations of EGCG at various time intervals which leads to raised bioavailability of EGCG by giving it with nutrients and quercetin.[25]

MDR transporters looked at the effect of CYP3A4 and P-gp dual inhibitor quercetin on the pharmacokinetics and bioavailability of the drug tamoxifen and one of its metabolites(4-hydroxytamoxifen) in rats. quercetin's ability to promote intestinal absorption and also stated that lessen tamoxifen's first-pass metabolism may be responsible for the enhanced bioavailability of tamoxifen as a result of its coadministration.[26]

Quercetin (bioflavonoid) inhibits p-glycoprotein and modifies plasma saquinavir concentrations. calculated Pharmacokinetic parameters using standard noncompartmental techniques and found that Plasma saquinavir concentrations were as same as quercetin administration.[27] The oral effect of quercetin on the bioavailability of diltiazem in rabbits. The bioavailability of diltiazem in the rabbits pretreated with quercetin is increased as compared to control, but not in the rabbits co-administered with quercetin.[28]

Naringin

It's a pure bio-enhancer that can be found in citrus fruits, particularly grapefruit. The fruit's bitter flavor is caused by the compound naringin. Between the flavanone naringenin and the disaccharide neohesperidose, the chemical structure contains a flavone-7-O-glycoside.[29] The main flavonoid glycoside present in grapefruit, apples, onions, and tea is naringin. Naringin has a wide range of pharmacological actions, including reducing blood cholesterol levels, antioxidant activity, antiulcer activity, antiallergic activity, and anticancer activity. Naringin has been noted to inhibit CYP3A4 and to modulate Pglycoprotein.[30]

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) consist of the first-line anti-retroviral medication

"efavirenz" and studied Naringin as a bioavailability enhancer and determined the Pharmacokinetic parameters of a combination of Efavirenz and Naringin. The absorption rate constant (Ka), elimination rate constant (K_{el}), C_{max}, $T_{1/2}$, and T_{max}, as well as the area under the curve, is increased.[31]

The impact of the CYP3A4 inhibitor grapefruit flavonoid naringin on the pharmacokinetics of quinine administered orally or intravenously to female Wistar rats. But after oral administration, peak plasma concentration (C_{max}), time maximum (T_{max}), and area under the plasma concentration-time curve (AUC) of quinine all increased with naringin. Pre-treatment with the naringin-rich grapefruit flavonoid increases the oral bioavailability of quinine in rats.[32]

The effect of naringin (flavonoid), on the pharmacokinetics of diltiazem and the active metabolite (desacetyldiltiazem) administered orally in rats in the presence and absence of naringin. The concomitant use of naringin increase the C_{max} and AUC of diltiazem by two folds pretreated and also raised the oral exposure of diltiazem in rats.[33] Verapamil was administered orally to rabbits pretreated with naringin, and the effect of naringin on the pharmacokinetics of verapamil and its nor verapamil (metabolites) in rabbits was examined. naringin pretreatment improved verapamil's oral bioavailability.[34]

To enhance the anticancer activity of Paclitaxel with Naringin in mixed polymeric micelles, Paclitaxel co-encapsulation with Naringin synergistically improved its intracellular uptake in mixed micelles and it is an effective strategy for achieving its higher anticancer activity.[35]

Genistein

It's a phytoestrogen and a member of the isoflavone flavonoid class. Numerous plants, including soybeans, fava beans, kudzu, and psoralea—serve as an important source of food. It is also present in coffee, Flemingia vestita, Flemingia macrophylla, and several medicinal plants.[36] The intestinal absorption of paclitaxel, a substrate for efflux transports like P-glycoprotein, BCRP, and MRP2, was significantly increased when co-administered with genistein and suppressed P-glycoprotein, BCRP, andMRP2 efflux function.[37]

prostaglandin (PG) is a pathway to treat prostate cancer (PCa) used a combination of calcitriol and genistein, both of which have antiproliferative properties.

He stated 3 separate ways of calcitriol to inhibit the PG pathway in PCa cells:

- decrease cyclooxygenase-2 (COX-2) expression,
- stimulate 15-hydroxyprostaglandin dehydrogenase (15-PGDH) expression, and
- decrease EP (PGE2) and FP (PGF(2alpha)) receptors

result in reduced levels of biologically active PGE2, leading to inhibit PCa cells. Genistein, an inhibitor of CYP24(enzyme) starts the calcitriol's degradation, which increases the bioactive calcitriol's half-life and improves all of the calcitriol's effects. Like calcitriol, it also inhibits COX-2 activity which decreased the synthesis of PGE2, inhibits the EP and FP receptors, and reduces the biological function of PGE2. The combination of calcitriol and genistein has an attractive therapeutic action for the treatment of PCa.[38] The anabolic effects of combining alendronate and genistein on osteoclastic results in potent and synergistic inhibition of RAW2674 cell proliferation and death also determined that bisphosphonate and genistein combination therapy might offer a cutting-edge method for preventing and treating osteoclastic bone resorption.[39]metformin(MET) and genistein are effective at reducing inflammation. MET and genistein, alone or in combination, may be used to treat high-fat diet (HFD)-induced skeletal muscle inflammation and to reduce weight gain, fasting blood sugar levels, plasma insulin, HOMA-IR levels, and area under the curves (AUCs) in the ipGTT. MET and genistein had a decreasing effect on the rate of macrophage infiltration, Expression of M2 macrophage markers increased even as iNOS expression was decreased. Likewise, genistein and MET increased the expression of IL-10 and decreased the expression of TNF-, IL-1, MCP-1, and IL-6.[40] According to research, Genistein's effects on anticancer drugs, Genistein enhanced cisplatin's anticancer activity in CaSki cells and increased the activity of a chemotherapy drug.[41] After oral administration of the anticancer medication paclitaxel in rats, genistein resulted in an increase in AUC and a decrease in total plasma clearance.[42]

Piperine

Piper longum and Piper nigrum, two species of the Piperaceae family of plants, exhibit the amide alkaloid piperine (1-piperoyl piperidine) and enhance the function commenced with the treatment of human tuberculosis.[43] After studying the pharmacokinetics characteristics of oxytetracycline collect blood samples from the wing vein and administered them orally with piper longum in white leghorn hens. measured the plasma concentration of OTC using a microbial assay technique with Bacillus cereus var. mycoides as the test organism, and findings suggest that AUC (area under the curve), AUMC (area under the first moment of plasma drug concentration-time curve), and MRT (mean residential time) are higher while the elimination rate constant and elimination half-life are reduced and increased.[44] Metronidazole with piperine's bioavailability investigated and determine the Cmax values of metronidazole alone and when combined with piperine. The peak plasma levels of metronidazole have risen, AUC increased, and a decrease in total clearance significantly increased the bioavailability of metronidazole.[45] The analgesic effects of Piper nigrum extract and its interactions with pentazocine and diclofenac sodium were examined in albino mice. In comparison to pentazocine, the tail flick latency increased significantly when Piper nigrum extract was added. According to the study analgesic effects of pentazocine and diclofenac sodium were enhanced by the Piper nigrum extract.[46] 1-peperoylpiperidine obtained from Piper nigrum Linn, inhibits the liver. Acetic acid-induced

writhing tests in mice using piperine signifying a dose-dependent synergistic effect on nimesulide-induced antinociception. The analgesic effect of submaximal nimesulide administration was improved by piperine and plasma concentration of nimesulide increased when piperine was added to the drug, which suggests that piperine slows the biotransformation and metabolism. The effect of piperine on carbamazepine in poorly controlled epilepsy patients by linking the pharmacokinetic parameters with the Students' t-test and resolved that Piperine expressively increased the mean plasma concentrations of carbamazepine, in AUC, Cmax, and t(max) i.e. Piperine enhances the oral bioavailability of carbamazepine, by decreasing the elimination and/or by increasing its absorption.[48] The effect of piperine on the bioavailability and pharmacokinetics of propranolol and theophylline stated that theophylline had a higher Cmax, longer elimination half-life, and a higher AUC. Additionally, in order to improve patient compliance and greater control over the therapeutic process, he researched clinical practice and increased the systemic availability of oral theophylline and propranolol.[49]

Curcumin

It is made up of both fresh and dried rhizomes from the Curcuma longa plant, which belongs to the ginger family. An ingredient, turmeric (Curcuma longa), is utilized as a treatment for a number of illnesses. To improve the bioavailability of celiprolol and midazolam in rats, curcumin, a flavonoid found in turmeric, blocks drug-metabolizing enzymes such as CYP3A4 in the liver and has the ability to modify the drug transporter P-gp. In tissues of the colon and liver, curcumin reduces UDP-glucuronyl transferase levels. Additionally, it alters the physiological processes taking place in the digestive system, which improves drug absorption.[50] The metabolic changes caused by the bioactive triterpenoids of Centell-S in combination with the enhancers piperine and curcumin in beagle dogs. As a result, the addition of piperine to Centell-S shows an increase in the bioactive triterpenoids that are linked to the biomarkers of neurodegenerative diseases which might be useful for neurodegenerative diseases.[51] Low levels of curcumin in plasma and tissues are primarily caused by poor absorption, faster metabolism, and rapid systemic clearance. The use of an adjuvant, complexed/encapsulated curcumin, particular curcumin formulas, and curcumin nanoparticles increased curcumin bioavailability. He focused on the efficacy of formulations based on curcumin in clinical studies and demonstrated that greater bioavailability results in greater therapeutic efficacy.[52] Quercetin increases drug bioavailability by inhibiting the Pgp efflux pump and metabolic enzymes. By increasing the absorption of curcumin in the intestinal lumen the enhancing characteristic (as an absorption enhancer) of quercetin. The increased concentration of curcumin indicates that quercetin is able to improve the absorption and bioavailability of the curcumin.[53] Curcumin is a yellow polyphenolic chemopreventive substance that was extracted from the Curcuma longa rhizomes. The liposomes' toxicity was assessed in a research environment, and mice with Dalton's ascites lymphoma were used to examine the liposomes' effectiveness in vivo. Mice with lymphoma responded better to quercetin-decorated liposomes than those without it in terms of duration of survival and weight gain. Quercetin was also a factor in the liposomal formulation's increased cytotoxicity toward HT-29 cells and HCT-15 cells.[54] Created solid lipid nanoparticles (SLNs) using tristearin and PEG-ylated emulsifiers to regulate the oral bioavailability of curcumin. The types and quantities of emulsifiers were changed to control the lipolysis of produced SLNs during simulated gastrointestinal digestion. Due to the neutral surface charge of the micelles, the curcumin loaded in long-PEGylated SLNs quickly pierced the epithelium, resulting in a >12.0-fold raised bioavailability when compared to curcumin solution in a rat model.[55] Stated Curcumin has poor bioavailability due to poor absorption, quick metabolism, and rapid systemic elimination, Therefore, he developed several strategies to improve the bioavailability, boost plasma concentration, and improve cellular permeability processes of curcumin using nanotechnologies such as liposomes, polymeric nanoparticles, micelles, nano gels, liposomes, cyclodextrins, dendrimers, and solid lipids.[56]

Aloe vera

It is dried juice that has been extracted through an incision from the bases of the leaves family Liliaceae—aloe species, including Aloe perryi, *Aloe vera* or Aloe barbadensis, and Aloe ferox. There are two alternative ways to prepare A. vera, whole leaf extract, and gel-filled interior, and both of these methods show enhanced absorption of both Vitamins C and E. A. vera was identified by several research as an incredibly potential future nutritional herbal bio-enhancer.[57]The efficacy of aloe solutions (whole leaf extract or inner fillet gel) on human's capacity to absorb vitamins C and E and observed that aloe gel raises levels of plasma ascorbate and plasma tocopherol for both vitamins. Aloes improve the absorption of vitamins C and E, and also increase their absorption.[58] For the gastroesophageal reflux symptoms *Aloe vera* and pantoprazole in mustard gas victims due to its cytoprotective effects on gastric mucosa through induction of endogenous prostaglandin production, and suggested an improvement in GERD symptoms in (SM)-exposed subjects.[59] *Aloe vera* was extracted using ethanol and increased the hypoglycemic effects of glipizide in streptozotocin-induced diabetic rats.[60] The bioavailability of vitamins C and $B_{(12)}$ in healthy human volunteers using two different *Aloe vera* preparations aloeleaf gel(AG) and aloe whole leaf decolorized gel(AL), and a placebo. AG greatly increased plasma oxygen radical absorbance capacity (ORAC) when combined with vitamins C and $B_{(12)}$. Plasma vitamin C and B_{12} were substantially raised by AG. Additionally, both aloes raised serum amounts of vitamin $B_{(12)}$. Because of their safety and tolerability, AG and AL formulations increase the bioavailability of vitamins C and $B_{(12)}$and their antioxidant potential.[61] streptozotocin (STZ)-induced diabetic rats, shown anti-hyperlipidemic efficacy of the ethanolic extract

from *Aloe vera* leaf gel. Fasting blood sugar, liver transaminases (aspartate aminotransferase and alanine aminotransferase), plasma and tissue (liver and kidney) cholesterol, triglycerides, free fatty acids, and phospholipids were all significantly decreased or improved after oral administration of *Aloe vera* gel extract. Plasma insulin was also significantly increased. [62] Due to its low aqueous solubility, the drug albendazole, which has a benzimidazole nucleus, is poorly absorbed from the digestive system. Aloe-emodin and quercetin, two phytoconstituents, were investigated and carried out an in-vivo research, looked into the pharmacokinetics and pharmacodynamic parameters, and concluded that albendazole's Tmax had not changed and that its Cmax values had changed significantly because quercetin contains flavonoids, albendazole's absorption was increased.[63] The buccal permeability properties of didanosine (ddI) and evaluated the potential of *Aloe vera* gel (AVgel) as a novel buccal permeation enhancer. This study demonstrates the potential of AVgel as a buccal permeation enhancer for ddI to improve anti-HIV and AIDS therapy.[64] It has been determined that one way to increase the oral bioavailability of macromolecular medications (such as protein and peptide drugs) is to co-administer absorption-enhancing agents with them. According to research by Haasbroek et al., some components of the *Aloe vera* leaf, such as the gel and whole leaf extract, may help drugs pass through the intestinal epithelial membrane more effectively.[65]

Zingiber officinale

One of the most significant elementary spices of India is ginger, which is the dried underground stem or rhizome of the zingiberaceous, herbaceous plant *Zingiber officinale* Linn. It has historically been employed as a digestive tract stimulant and carminative. It is very popular as a home treatment for colic and flatulence. Ginger is applied externally as a rubefacient and local stimulant. The following sorts of chemicals are typically found in ginger oleoresin (Gingerin), including volatile oils, resins, phenols, gingerols, gingerones, and shogaols. Sesquiterpene hydrocarbons (at least 50%), sesquiterpene alcohols, monoterpenoids and related chemicals, acetic acid, and caprylic acid esters, as well as traces of chavicol, are all present in the oil. Ginger's job is to control intestinal activity to promote absorption.[66] The bioenhancer extract's effective dose ranges between 10 and 30 mg/kg body weight. Atazanvir's bioavailability was found to be enhanced by piperine and ginger oleoresin when used in combination with ritonavir. When combined with atazanavir (ATV), piperine (30 mg/kg) has been found to improve the bioavailability of both dosages of ATV. Piperine increases atazanavir's activity.[67] The bioavailability of several classes of antibiotics, including azithromycin, erythromycin, cephalexin, cefadroxil, Amoxycillin, and cloxacillin, was significantly increased. [66] Gingerol, controls GI tract activity and improves absorption. It increases the bioavailability of rifampicin by 65% and ethionamide by 56%. Additionally, it improves the bioavailability of medications (such as the anticancer agent 5-fluorouracil, the antifungal ketoconazole, and the antibiotic azithromycin, respectively).[68]

Nitrile glycoside

The pods of the Moringa oleifera plant, classified as a member of the Moringaceae family, the biological source of nitrile glycosides and its byproducts. They do not have their own drug activity, but they can boost biological activity and increase drug absorption in combination therapy. Ampicillin, rifampicin, and tetracycline are just a few of the regularly used antibiotics that the nitrile glycoside, like niaziridin, has improved the absorption.[69] The increasing bioactivity of widely used antibiotics like rifampicin, tetracycline, and ampicillin and makes it easier for medications, vitamins, and nutrients to be absorbed through the gastrointestinal barrier, boosting their bioavailability.[70] By using bioactivity-guided splitting to extract a novel nitrile glycoside named NIAZIRIDIN, improved the bioactivity of common antibiotics like rifampicin, tetracycline, and ampicillin against Gramme (+) and (-) bacteria. Also increased the absorption of medications, vitamins, and nutrients through the gastrointestinal membrane, thereby increasing their bio-availability. Therefore, niaziridin can be used in combination therapy with medications and nutrients, reducing the side effects of the drugs, as well as the cost and duration of chemotherapy.[71] About the Moringa leaves and showed the structural needs of an immunostimulating polysaccharide and niaziminin, both of which have to prevent tumor promoter-induced Epstein-Barr virus activation.[72]

Lysergol

The morning glory family of plants (Convolvulaceae), which includes the hallucinogenic seeds of Rivea corymbosa, Argyreia nervosa, and Ipomoea violacea, contain this alkaloid. as it contains dimethylarginine, also known as clavine, derivative.[73] Lysergol could boost the bioavailability of some broad-spectrum antibiotics. A potential herbal bioenhancer Phyto molecule called lysergol (9, 10-Didehydro-6-methylergoline-8--methanol) is derived from the morning glory plant (Ipomoea spp.), which increases the antibacterial effects of various antibiotics. It has been isolated from higher plants like Ipomoea muricata, Rivea corymbosa, and Ipomoea violacea. Ipomoea muricata seeds are a good source of clavine alkaloids.[74] Under normal circumstances, lysergol keeps the blood flowing and According to when medications are also provided, it tends to increase their biological activity by facilitating transfer over the membrane to the target region.[75] lysergol increased the bioavailability of berberine in Sprague-Dawley rats after oral treatment. When lysergol was present, the plasma content of berberine increased Therefore, lysergol significantly increased berberine's bioavailability while leaving the drug's absorption and elimination properties unaltered. The enhancement could be achieved by blocking berberine's metabolism or altering how it crosses cell membranes.[76]

Table 1: Application of Combination of Natural Bioenhancers and Drugs

Bioenhancers	Description	References
Quercetin with Curcumin	Increase in bioavailability and $t_{1/2}$, as well as decrease in clearance.	16
Quercetin With Berberine chloride	Improves the ex vivo permeability which increases its bioavailability and reduces the dose resulting in improved patient compliance.	17
Quercetin and losartan	The C_{max} and the AUC of losartan improved ($p < 0.05$), and the C_{max} of EXP3174 reduced.	18
Quercetin with midazolam	Reduce systemic exposure to the orally given drug by increasing its CYP3A-catalyzed metabolism	19
Quercetin with glimepiride	Increased Cmax, AUC0-n, AUC total, $t_{1/2}$, MRT, and decreased clearance, reduce glucose levels in diabetic rats.	20
Quercetin with Clopidogrel	Increase in the peak plasma concentration	24
Quercetin with Epigallocatechin gallate	Raised bioavailability of EGCG	25
Quercetin with Tamoxifen	Promote intestinal absorption, and enhanced the bioavailability of tamoxifen.	26
Naringin With Efavirenz	The absorption rate constant (K_a), elimination rate constant (K_{el}), C_{max}, $T_{1/2}$, and T_{max} as well as the area under the curve is increased.	31
naringin with quinine	Peak plasma concentration (Cmax), time maximum (Tmax), and area under the plasma concentration-time curve (AUC) of quinine all increased with naringin, naringin-rich grapefruit flavonoid increases the oral bioavailability.	29
naringin(flavonoid) with diltiazem	Increase the C_{max} and AUC of diltiazem	28
Naringin with Verapamil	Improved verapamil's oral bioavailability.	34
Paclitaxel with Naringin	Synergistically improved its intracellular uptake in mixed micelles.	35
Calcitriol with Genistein	Genistein, an inhibitor of CYP24(enzyme) starts degradation and increases $t_{1/2}$.	38
Genistein with Aendronate	Genistein on osteoclastic shows potent and synergistic inhibition of RAW2674 cell proliferation and death.	39
Genistein and Metformin	Treat high-fat diet (HFD)-induced skeletal muscle inflammation and reduce weight gain, fasting blood sugar levels, plasma insulin, HOMA-IR levels, and area under the curves (AUCs) in the ipGTT.	40
Genistein and cisplatin	Anticancer effect in CaSki cells and boosting the activity of a chemotherapeutic agent.	41
Piperine and blood sample from wing vein	AUC (area under the curve), AUMC (area under the first moment of plasma drug concentration-time curve), and MRT (mean residential time) are higher while the elimination rate constant and elimination half-life are reduced and increased.	42
Piperine with Nevirapine	Nevirapine is a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase and inhibits drug metabolism thus increasing the bioavailability and effect of some drugs.	77
Metronidazole with piperine	The peak plasma levels of metronidazole have risen, AUC increased, and decrease in total clearance.	44
Piperine extract and pentazocine and diclofenac sodium	Pentazocine, the tail flick latency increased significantly when Piper nigrum extract was added.	46

Piperine and Nimusulide	Piperine signifies a dose-dependent synergistic effect on nimesulide-induced antinociception. piperine slows biotransformation and metabolism.	47
piperine and carbamazepine	Piperine enhances the oral bioavailability of carbamazepine, by decreasing the elimination and/or by increasing its absorption.	48
Piperine and propranol, theophylline	Clinical practice and increased the systemic availability of oral theophylline and propranolol.	51
piperine and curcumin	The efficacy of formulations based on curcumin in clinical studies demonstrated that greater bioavailability results in greater therapeutic efficacy.	52
Quercetin and curcumin	The increased concentration of curcumin indicates that quercetin is able to improve the absorption and bioavailability of the curcumin.	53
Quercetin and curcumin	Quercetin also contributed to enhanced cytotoxicity of the liposomal formulation towards HT-29 cells and HCT-15 cells.	54
Quercetin and curcumin	Curcumin loaded in long-PEGylated SLNs rapidly permeated the epithelium due to the neutral surface charge of the micelles, resulting in a >12.0–fold increase in bioavailability compared to curcumin solution in a rat model	55
Quercetin and curcumin	improve the bioavailability, increase the plasma concentration, and enhance the cellular permeability processes of curcumin.	56
Aloe vera and vitamins C and E	Aloes improve the absorption of vitamins C and E, and also increase their absorption.	57
Aloe vera and pantoprazole	Improvement in GERD (Gastroesophageal reflux disease)symptoms in (SM)-exposed subjects.	59
Aloe vera and glipizide	Increases the hypoglycemic effects. streptozotocin-induced diabetic rats.	60
Aloe vera and ethanolic extract	Increase the STZ effect and antihyperlipidemic efficacy.	62
Aloe vera and chitosan	Aloe vera and chitosan greatly extended the storage life of chitosan.	78
Alovera and vitamins C and B_{12}	AG and AL formulations increase the bioavailability of vitamins C and B(12) and their antioxidant potential.	61

OBSTACLES WITH BIOENHANCERS

The prospect of a bioenhancer is currently a highly demanded one throughout society, but there are still many issues with research and development that need to be overcome before these products can be successfully marketed. The difficulty lies: in enhancing the medication's physicochemical properties and its delivery system to ensure lengthy blood circulation, drug protection, and site-specific targeting. The stability and effectiveness of the drug carrier system may be impacted by increasing the surface area of the system. Increasing the manufacture of bio-enhanced medication delivery devices presents another difficulty. Due to difficulties like low nanoparticle concentrations, agglomeration, and the requirement to alter chemical procedures for production at commercial scales, this can be challenging. For the manufacture of these systems to be efficient and effective, pilot approaches and scale-up processes must be created. Because bio-enhanced drug products do not yet have standardized physicochemical and pharmacokinetic properties established, regulatory control is another challenge. Similar to what the US-FDA and EMEA have established for conventional medical goods, regulatory agencies must take the initiative to establish criteria and guidelines for the development and approval of enhanced drug products.[88,89,90]

FUTURE ORIENTATION

By using bio-enhancers, the dose requirement can be reduced, and also lowering the risk of drug resistance as well as the accompanying side effects. By using bio-enhancers, the likelihood of their toxicity can be reduced. Despite the fact that many medicines—including the chemotherapeutic drug taxol—can be very helpful, they also have serious side effects and toxicity. Less prescriptions are required when the dosage is reduced, which reduces costs as well. Therefore, the use of bio-enhancers in modern medicine may lead to the development of drugs that are better, safer, and more effective.

Needs for bioavailability enhancers

The concept of bio-enhancers is novel and was inspired by an antiquated Indian medicinal system. They will lessen the price, toxicity, and other negative effects of pharmaceuticals while improving the economy of the country. A rise in the number of medical advancements also means a rise in the variety of negative effects they induce. By utilizing bio-enhancers, the dose can be drastically reduced, helping to reduce the likelihood of negative effects. Even though some plant extracts and phytoconstituents exhibit incredible bioactivity *in vitro*, their ineffective lipid solubility, inappropriate atomic size, or a combination of the two results in poor absorption and bioavailability. It was discovered that there was a loss of specific bio-activity when individual ingredients from the plant extract were constrained. When consumed orally, a multi-constituent plant extract may occasionally have some components destroyed in the stomach. They reduce the dosage, shorten the course of treatment, and as a result, drug resistance problems are lessened. The dose economy makes treatment cost-effective and reduces drug toxicity and adverse reactions.

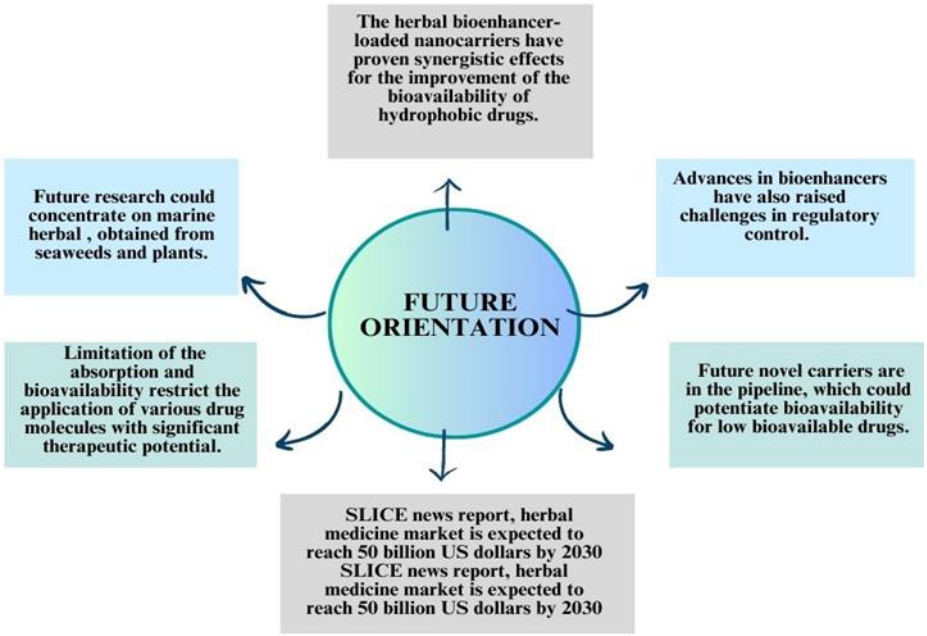

Table 2: Fabrication of dosage form using natural bio-enhancers

Sr no	Herbal bio enhancer	Drug	Dosage form	Objective	Ref
1	Naringin	atorvastatin calcium	bilayer tablet	The bioavailability of atorvastatin has improved.	79
2	Piperine	Natural Polymers	Fast Dissolving Tablet	Increase the bioavailability of therapeutic moieties and decrease dosing requirements.	80
3	Curcumin	HPMC	unidirectional, bilayered, mucoadhesive tablet	Potential to bypass the first-pass metabolism and improve the bioavailability of curcumin.	81
4	Quercetin	paclitaxel	Enteric-coated tablets	An easy, fast, and validated RP-HPLC method was invented to quantify paclitaxel in drug solution and orally disintegrating tablet.	82
5	Piperine	acyclovir	Capsules	Acyclovir formulation demonstrated the capacity to sustain acyclovir plasma concentration for up to 24 hours, as opposed to drug solution, which could only do so for 4 hours.	83
6	Aloe vera	protein and peptide drugs	*Aloe vera* gel	Various components of the Aloe vera leaf, such as gel and the entire leaf extract, have demonstrated the ability to improve medication penetration through the intestinal epithelial barrier in earlier investigations.	84
7	Quercetin	Rifampicin	Floating microsphere	Improved Stability and In-vitro Drug Release	85
8	Bile salt	Dunaliella salina	oral tablets	D. salina powder bio-enhanced oral tablets offer an encouraging antifibrotic potential against TAA-induced fibrosis in rats.	86
9	Aloe vera	Opioid analgesic	Nasal spray	Enhanced decongestant and antihistamine properties caused by saponin.	87

CONCLUSION

Ayurveda had a clear definition of the novel and revolutionary idea of bio-enhancer, which it had long since put into practice. Combining modern medical research with the idea of natural bio-enhancers can result in an ideally revolutionary drug delivery system that can lower drug costs by lowering the dosage required, reducing toxicity, lessening side effects, and bringing numerous additional advantages. Formulations with natural enhancers that improve the bioavailability and effectiveness of the active components open up fresh prospects for the pharmaceutical and healthcare industries. Currently, a lot of research is being done on various classes of bioactive for their potential to improve pharmaceutical formulations.

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