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Review Article

Herbal Bioenhancers with Nanocarriers: A Promising Approach for Oral Peptide Delivery

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ABSTRACT

The oral delivery of protein and peptide drugs faces immense challenges due to the harsh gastrointestinal (GI) environment, large molecular size, and low stability. Even though different approaches are employed to deliver peptide drugs efficiently, they have limited success. Recently, the use of nanoparticles as carriers for peptides as a means of surmounting the gastrointestinal barrier and as an effective alternative to parenteral administration has gained much attention. It is often necessary to supplement this mode of delivery by using strategies such as permeation enhancers. Bio-enhancers play a significant role in reducing the dose, drug resistance, toxicity, and treatment expenses. The potential of herbal bio-enhancers as a safe and effective substitute to non-herbal permeation enhancers in improving oral absorption of peptides from nanoparticulate systems has been explored recently. Piperine is counted first in the list of bio-enhancers and can improve the bioavailability of peptides and other drugs. Other molecules like naringin, glycyrrhizin, quercetin have great significance either alone or in combination in improving the oral bioavailability of drug molecules. Bioenhancers are beneficial for drugs with poor lipid solubility and large molecular size, causing poor absorption and low bioavailability. Herbal bioenhancers can decrease the dose, drug resistance, toxicity, adverse effects, and overall treatment cost as they are inert, easily procured and economical. This review article focuses on the significance of nanoparticles in the oral delivery of peptide drugs and the vital role played by herbal bioenhancers in their absorption from the GI tract.

Keywords: Bio-enhancer, Herbal, Peptide drug, Nanoparticles, Bioavailability.

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INTRODUCTION

Protein and peptide drugs have been widely used for the management of several diseases. Cancer, cardiovascular diseases, autoimmune disorders, and diabetes are a few conditions that have benefited significantly from peptide drugs. Compared to chemically synthesized small drug molecules, they have high efficacy and specificity and hence are considered promising macromolecules in drug development.[1] The biological activity of these macromolecules is attributed to their complex structure, which unfortunately is also responsible for their liabilities in formulation and delivery.[2] Poor permeability of macromolecules through biological barriers and loss of their activity arising from the effect of pH, temperature, and moisture *in vivo* and *in vitro* are major challenges in formulation.[3] Consequently, peptide drugs are administered mainly as injections but face drawbacks such as pain, needle phobia and requirements for sterile production. Many biopharmaceuticals are rapidly eliminated from the body and require frequent administration, leading to poor patient compliance.[2]

The oral route for the administration of such hydrophilic macromolecules is fraught with problems such as destruction by stomach acids, enzymatic degradation and poor permeability across the intestinal barrier, all of which give rise to poor oral bioavailability.[4] Peptide drugs show <1% bioavailability on oral administration because of the three barriers in the GI tract, namely the mucus, intestinal and enzyme barriers. The mucus barrier is a viscous layer of definite thickness covering the entire surface of the GI mucosa and is secreted by the goblet cells of the intestinal epithelium. It comprises mucin, enzymes, electrolytes, and water and can be a barrier to drug diffusion and absorption.[5] The intestinal barrier is constituted by the tight intercellular junctions between the epithelial cells that block the paracellular pathway for hydrophilic drugs.[6] The principal reason for the poor

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oral bioavailability of peptides is their extremely poor permeability across the intestinal epithelium due to large molecular weight and high hydrophilicity. Hence efforts must be made to improve the permeability of these macromolecular drugs. The enzyme barrier is constituted by the various proteolytic enzymes responsible for the degradation of the drugs into small peptides or amino acids.[7] However, if these complications are resolved, the oral route would be the most preferred with improved patient compliance, ease of scale-up, pack and handle than liquid injections.[8] Oral delivery of protein and peptide drugs can significantly reduce health care costs and could improve the quality of life.

Several efforts have been reported for the development of oral peptide delivery systems. These approaches have been designed to surmount one or more of the three barriers described earlier and are based on the principles of stabilization, mucus penetration/adhesion and permeation enhancement. Accordingly, some of the techniques that have been explored are pH modulation, enzyme inhibition, enteric coating, microencapsulation, mucus penetrating systems, mucoadhesive systems, prodrugs, absorption enhancers, intestinal microneedles and nanocarriers.[9] Among these strategies, nanoparticles are more promising since they can protect the drug from premature degradation and inactivation, with excellent intracellular penetration and potential for enhanced drug absorption. The most widely used approach is employing permeation enhancers or absorption enhancers to improve the intestinal permeation of macromolecules.

While developing a viable oral delivery system for protein and peptide drugs, physicochemical properties like pH, molecular weight and size, hydrophobicity, and biological barriers must be thoroughly considered.[10] The bioavailability of protein and peptide drugs depends on their capability to cross the intestinal mucosa to enter the systemic circulation.

This review aims to offer a comprehensive overview of published research where bioenhancers have been investigated in the oral delivery of peptide drugs and those that could be promising along with the challenges involved.

Nanoparticles as Carriers for Oral Peptide Delivery

In recent years, research towards developing an effective and stable oral formulation has leaned mostly towards nanotechnology. Many reviews that have been published discuss the strategies and approaches that can be used to improve the oral delivery of peptides and protein drugs by nanoparticles.

Nanoparticles help overcome many of the barriers associated with the oral administration of peptides, including enzymatic degradation and poor membrane permeability.[11] By suitable formulation, nanoparticles can be designed to protect the drug from premature degradation and interaction with the gastrointestinal environment by entrapping the drug within the polymer matrix or core. They also increase intracellular penetration and enhance drug absorption.[12] They improve the distribution of the drug at the intestinal epithelium. However, the protective mucus coating on the intestinal membrane surface could act as a barrier to the permeation of drugs.[13] The use of mucoadhesive and mucus-penetrating nanoparticles have been reported to be promising in overcoming this barrier. Self-assembled nanoparticles for oral insulin delivery have achieved excellent mucus permeation when coated with N-(2-hydroxypropyl) methacrylamide copolymer.[14]

An essential advantage of using nanoparticles for the oral delivery of peptides is that they are capable of endocytic uptake by the M cells of the Peyer's patches, located in the intestinal mucosa. This site is known to take up macromolecules into the systemic circulation and transport them through the biological mucosa in their entirety.[15] Physicochemical properties of particles such as size, zeta potential, attached ligands or surface hydrophobicity decide their endocytic uptake. Particles of size between 50 - 100 nm are transported while larger particles are entrapped in the Peyer's patches. Charged particles tend to be transported less due to electrostatic repulsion and mucus entrapment. By virtue of their small size, increased surface area, and high membrane adhesion, nanoparticles accumulate in the Peyer's junction, where they may be engulfed into the systemic circulation along with their peptide payload, thereby improving their bioavailability.[16]

Research has shown that the intestinal absorption of nanoparticles can be further enhanced. The strategies for improving the oral bioavailability of nanoparticles of peptide drugs include the use of permeation enhancers, enzyme inhibitors, mucoadhesive polymers,[17] ligand modification, cell-penetrating peptides[18] and colon-specific delivery.[19] Studies show that when permeation enhancers are combined with nanoparticle technology, there is a substantial increase in drug absorption.[20] Nanocarriers can also be decorated with ligands to enhance oral absorption further.

The physicochemical properties of nanocarriers such as type of polymer or carrier material, particle diameter surface properties, surface charge and surface modifications can significantly influence the success of these formulations in the oral delivery of peptide drugs.

The efficiency of these nanocarriers can be further improved by the inclusion of specific additives in the formulation or by utilizing certain approaches to aid in the absorption or permeation of the former through the GI barrier. Some of these approaches that have been reported from recent studies are the use of enzyme inhibitors, mucoadhesive polymers, cell-penetrating peptides and permeation enhancers or bioenhancers as represented in Figure 1.[21]

Enzyme Inhibitors (EI)

EI's can protect the therapeutic peptides from luminal breakdown caused by various proteases like pepsin, trypsin, chymotrypsin.

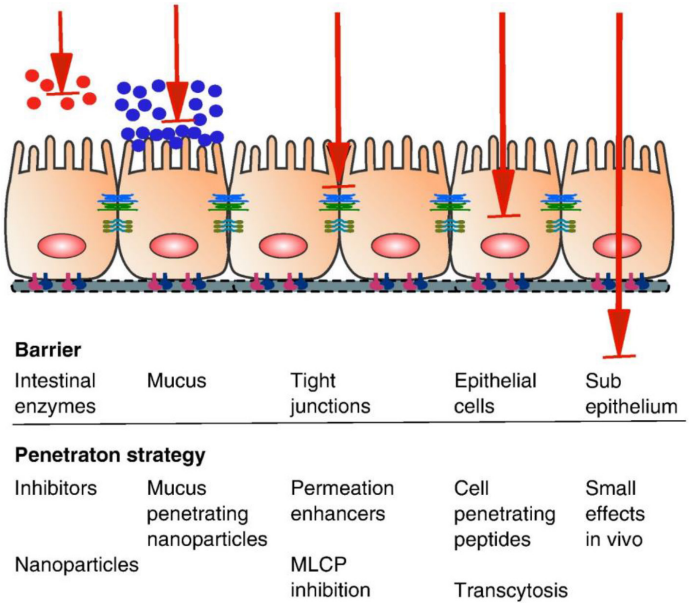

Figure 1: Gastrointestinal barrier for oral delivery of peptide drugs with strategies to overcome the same.[21*]
Note: The arrows indicate the extent of permeation of particles; the red spheres represent nanoparticles degraded or destroyed by the gastrointestinal enzymes, and the blue spheres are particles that are restrained by the mucus layer.
*Reproduced from Journal of Advanced Drug Delivery Reviews 106 (2016) 256-276

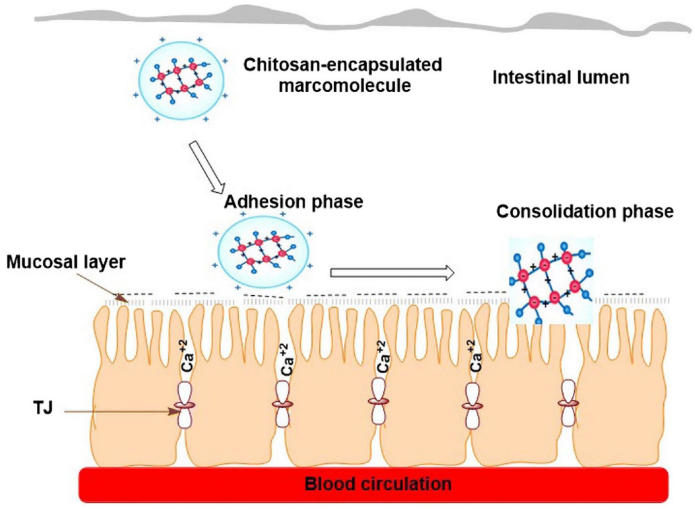

Figure 2: The attachment and consolidation stages of a chitosan-based mucoadhesive nanoparticle showing the adhesion and consolidation phase. TJ - tight junction; Ca+2 - calcium ion[23]
*Reproduced from DARU Journal of Pharmaceutical Sciences 28, 403–416 (2020)

Numerous enzyme inhibitors like alpha chymotrypsin inhibitors, amastatin, soybean trypsin inhibitors, pancreatic inhibitors, puromycin, aminopeptidase inhibitors are employed to counter the effect of these enzymes. Positive effects of oral insulin delivery by co-administering with specific enzyme inhibitors are already reported. Combining enzyme inhibitors with permeation enhancers can improve the bioavailability of peptide drugs to a greater extent as it promotes enzyme inhibition and absorption enhancement through the intestinal membrane. The use of EI's for long-term usage is not recommended as they can rupture the integrity of the mucosal surface and interact with dietary proteins, increase the drug concentration at the site of absorption without crossing biological membranes, and affect the absorption of other proteins that are normally degraded. Another disadvantage associated with the use of EI's is that they are not site-specific, which will adversely affect the metabolic pattern in the GI tract because of the decreased digestion of food proteins.[22]

Mucoadhesive polymers

They can be used to prolong the residence time of the drug at the absorption site by increasing the mucosal contact, thereby increasing the drug concentration. They not only have mucoadhesive properties but also can act as protease inhibitors and permeation enhancers. Their ability to adhere to the mucosal epithelium helps in improving the oral bioavailability of protein and peptide drugs. They also reduce the rate of clearance of drug molecules from the absorption site, thereby increasing the time available for absorption, offering controlled release and reducing the frequency of drug administration. Mucoadhesive polymers are synthetic or semi-natural. Chitosan is the best example. The ability of chitosan to transport a peptide molecule is illustrated in Figure 2.[23] Other examples include Carbopol, polyacrylate, carboxymethyl cellulose, hydroxypropyl cellulose, polyvinyl alcohol. Thiolated polymers are more suitable mucoadhesive polymers for hydrophilic macromolecules, they form strong covalent bonds with mucus membranes, but they possess low stability.[23,24]

Cell-penetrating Peptides (CPP)

CPP's are short peptide sequences with positively charged amino acid fragments that can enhance the absorption of therapeutic peptides and help to improve their pharmacokinetics by formulating them as different drug delivery systems. They have suitable membrane penetrating ability and can carry macromolecules into the cells, but the exact mechanism is unclear. They may be directly crossing the cell membranes or by the formation of channels or endocytosis. Some CPP's on simple mixing with molecules like insulin can enhance its intestinal absorption; they also form covalent bonds with these macromolecules to improve their absorption. CPP's when covalently conjugated with insulin, enhance insulin permeation across Caco-2 cell monolayers. CPP's like polyarginine, penetratin can act as a carrier for insulin, glucagon-like peptide, gastrin, interferon-β. Some examples of CPP's are penetratin, oleoarginine, and transportan.[20,25]

Permeation Enhancers (PE)

PE or permeation enhancers are excipients often used in formulation, whose function is to increase absorption by

enhancing membrane permeation rather than increasing solubility.[26] These compounds can alter the membrane structure and have been investigated for at least two decades in developing non-injection formulations for peptides, proteins, and other pharmacologically active compounds that have poor membrane permeability.

The use of PE facilitates both paracellular and transcellular pathways by modulating absorptive epithelium characteristics. In the paracellular pathway, they open the tight junctions, whereas, in the transcellular pathway, they increase the permeability of the plasma membrane.[27] Calcium chelators act by loosening the attachments of tight junctions through calcium depletion.[28] Surfactants disrupt the barrier function of the epithelium. The effectiveness of PE's is not the same along the GI tract because of the differences in membrane thickness, cell morphology, proteolytic activity, lipid compositions, and protein interactions. Application of PE's can break the intestinal barrier by changing the cell integrity of tight junctions and enlarging intercellular spaces by disrupting the lipid bilayers, resulting in holes forming and enhancing the absorption via the GI tract into the blood.[29]

Bile salts, chelators, surfactants, fatty acids, cationic and anionic polymers are some of the categories of permeation enhancers commonly used. Other examples are EDTA, sodium salicylate, chitosan, phenyl piperazine, sodium dodecyl sulphate, which have different mechanisms. The flip side of using PE is that long term usage can damage the biomembrane and result in local inflammation. They can because toxic substances to be absorbed into the circulation, increase systemic exposure to dietary antigens and even lead to autoimmune diseases. The use of PE's must be avoided in patients suffering from irritable bowel disease, celiac disease, and inflammatory bowel disease; hence they are more suitable for localized delivery systems like hydrogels.[19]

On the other hand, PEs of plant or animal origin have been found to possess a non-toxic safety profile, efficient even at lower concentrations, and compatible with formulation excipients. That is why there has been an interest in using PE of natural origin, which is considered a more attractive option. This review will focus on bioenhancers of herbal origin.

BIO-ENHANCERS

Herbal medicines have always enjoyed popularity worldwide due to their therapeutic actions and low side effects when compared to chemical drug molecules. In an attempt to find permeation enhancers that were safer recently, there has been a shift towards herbal constituents that could have the same effect. Bio-enhancers or Bioavailability enhancers are molecules of natural origin that are capable of increasing the rate and/or extent of absorption of the co-administered drug molecules into the systemic circulation, unchanged. Thus, these herbal constituents improve the bioavailability and efficacy of drugs with which they are combined without exerting any pharmacological action of their own. Hence the term, 'bio-enhancer' was coined.[30] Indian scientists at the Indian Institute of Integrative Medicine, Jammu, are credited with discovering and validating the world's first bioavailability enhancer, Piperine, in 1979.[31]

In addition to improving membrane permeability, these compounds are also non-toxic, pharmacologically inert, economical and easily procured. In the Ayurvedic system of medicine, a combination of black pepper, long pepper, and ginger, collectively called 'Trikatu', was used as a component in herbal formulations. It was observed that either 'Trikatu' or one of its ingredients appeared to enhance the efficacy of the Ayurvedic formulation. The bio-enhancing action of long pepper was first documented by Bose, who found that the anti-asthmatic effect of Vasaka leaves was enhanced when long pepper was combined with it.[32]

Many mechanisms of action of bio-enhancers have been postulated. These include modifying GIT epithelial cell membrane fluidity and permeability to increase passive transcellular drug permeation; promoting paracellular diffusion by relaxation of tight intercellular junctions; active efflux transporter modulation, such as P-gp-related efflux inhibition; suppressing first-pass hepatic metabolism by inhibiting cytochrome P450 (CYP) metabolizing enzymes; reduction in hydrochloric acid secretion; increasing gastrointestinal blood supply; and inhibiting GI transit and gastric motility.[33,34] The use of natural bio-enhancers can improve the pharmacokinetic parameters of many drugs. Molecules like piperine, glycyrrhizin, quercetin, naringin, genistein have shown marked effects in enhancing the bioavailability of many drugs. The need for a bioenhancer arises mainly for drugs with poor lipid solubility and large molecular size, causing poor absorption and low bioavailability. The gastric environment on oral administration destroys these drugs.[35]

Piperine

Piperine is counted first in the list of bio-enhancers and can improve the bioavailability of Ayurvedic, Allopathic and Unani drugs. It is considered the world's first bioenhancer. Piperine is a vital alkaloid present in *Piper nigrum* (Black pepper) and *Piper longum* (Long pepper) of family Piperaceae possessing many medicinal properties as well as shown bioavailability enhancement of many drugs.[31]

Mhaske DB *et al*. reviewed the effect of piperine as a bio-enhancer in improving the bioavailability of many drugs. They discussed the mechanism of action, inhibition of metabolism, and drugs bio enhanced by piperine and analyzed that the formulations with a bioenhancer like piperine are more effective when compared to the ones without it. Piperine enhances the C_{max} of many drugs significantly. Piperine at a dose of 15mg/person/daily and not exceeding 20mg/daily in divided doses can exert a bio-enhancing action. The effective bio-enhancing dose varies, 10%w/w of the active drug is generally considered as the bio-enhancing dose

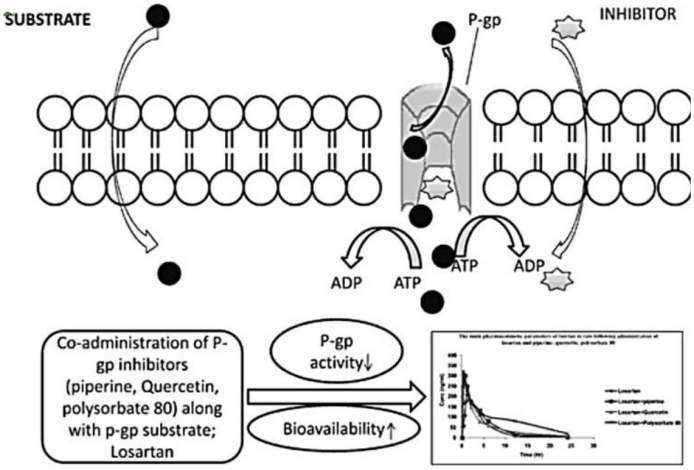

Figure 3: Mechanism of inhibition of P-gp efflux transporters by bioenhancers such as piperine.[37]
*Reproduced from Journal of Pharmaceutical Nanotechnology 2014;2:49–55

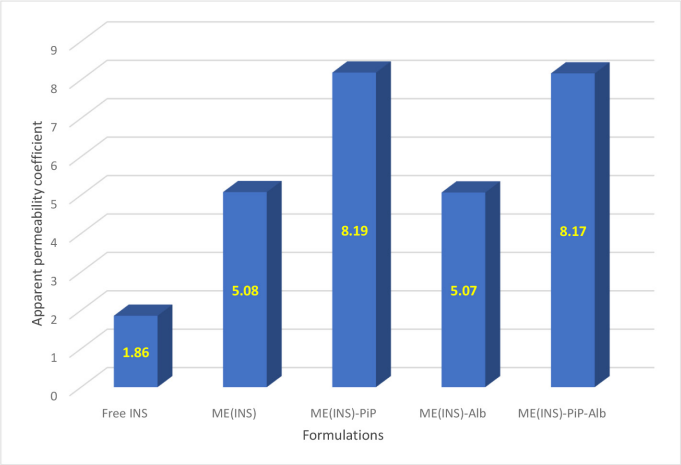

Figure 4: Apparent permeability coefficient of insulin released from various formulations across intestine.[38]

for most drugs.[36] Atal suggested that piperine can accelerate the absorption of many drugs by overcoming the drug metabolism and protecting the drug and by enhanced absorption through GIT or a combination of both approaches. Piperine inhibits P-glycoprotein, UDP glucoronyl transferase enzyme, and Cytochrome P-450 (CYP 450), CYP1A1, CYP1B1, CYP1B2, CYP3A4, CYP2E1.[31] Piperine enhances the efficacy of many drugs like phenytoin, dapsone, curcumin, ciprofloxacin, rifampicin, propranolol. The mechanism of inhibitions of P-glycoprotein enhancers is represented in Figure 3.[37] Piperine interacts with metabolizing enzymes resulting in oxidation, hydroxylation, glucuronidation.[31] Microemulsion (ME) (w/o/w) was designed by Kaur *et al*. with piperine as a permeation enhancer and albumin as a stabilizer for the oral delivery of insulin. They observed a significant variation in insulin permeability in *ex vivo* intestinal permeability studies (Figure 4). Insulin ME with piperine and albumin showed four and 1.5 fold enhanced permeation compared with free insulin and ME without piperine, respectively, which clearly explained the role of piperine as a permeation enhancer.[38] A combination of bio-enhancers like piperine, fulvic acid, lysergol to enhance the intestinal permeability of hepatoprotective drug silymarin by Javed S *et al*. observed that the absorption transport of silymarin is significantly increased in the presence of piperine-fulvic acid combination.[39] Piperine analogues were found to enhance the oral bioavailability of etoposide by inhibiting P-glycoprotein and CYP 3A4.[40] Risorine, a combination of 200mg rifampicin, 300mg isoniazid with 10 mg piperine decreased the dose of rifampicin and successfully completed all the clinical trials. Piperine increased the peak plasma levels of metronidazole by 57% with an increase in plasma half-life from 11.48-12.24 hr.[41]

Glycyrrhizin

Glycyrrhizin is a saponin glycoside present in glycyrrhiza glabra. It mainly acts by inhibiting the P-glycoprotein efflux pump. Glycyrrhizin acts as a bioenhancer in the concentration range from 0.05 to 50%. It improves the efficacy of drugs like rifampicin, nalidixic acid, tetracyclines, ampicillin, vitamin B1, B12, etc. It prolongs the bioavailability of rifampicin by six times at a concentration of 1 µg/ ml and that of Taxol by five times. Glabridin, a metabolite of liquorice, inhibits CYP3A4, 2B6 and 2C9, and glycyrrhetinic acid inhibits CYP3A, 2C9 and 2C19. Glycyrrhizin is effective against dose-dependent side effects of chemotherapeutic agents and resistance development against antimicrobial agents. Glycyrrhizin will be converted to glycyrrhetic acid by β-glucuronidase, which improves its absorption-enhancing activity. It can enhance the bioavailability of drug molecules by permitting them across biological membranes, hence increasing their plasma levels.[42]

Genistein

Genistein is a phytoestrogen found in dietary plants like soybean and kudzu. It is a P-gp inhibitor. It is reported that it also suppresses MRP2 and BCRP efflux functions. 10 mg/kg of genistein cause an increase in AUC and a decrease in total plasma clearance of paclitaxel on oral and IV administration. Genistein also increases the bioavailability of epigallocatechin gallate by increasing the C_{max}, AUC and $t_{1/2}$ by 2, 4.7 and 1.4-fold in mice.[43]

Quercetin

Quercetin, a flavonoid glycoside, is present in citrus fruits. It increases the bioaccumulation, drug concentration, and effectiveness of many drugs like diltiazem, digoxin, paclitaxel, doxorubicin, tamoxifen. Plasma concentration, AUC, C_{max} of diltiazem in rabbits treated with quercetin higher than untreated rabbits. CYP3A4 metabolises diltiazem, and P-glycoprotein inhibits absorption. Enhanced AUC, C_{max} of diltiazem treated with quercetin may be due to the inhibition of CYP3A4 and P-glycoprotein. Quercetin also enhances the bioavailability of epigallocatechin gallate, an anticancer component present

in green tea, with low oral bioavailability in humans and rats. A study done by Manodeep Chakraborty *et al*. observed the potential of quercetin as a bioenhancer for curcumin for treating ischemia-reperfusion injury-induced myocardial toxicity in rats. A remarkable enhancement in bioavailability as well as half-life with decreased clearance was observed with quercetin.[44] Quercetin enhances the bioavailability of tamoxifen and 4-hydroxytamoxifen when given orally in rats. It inhibited the first-pass metabolism of tamoxifen and a remarkable rise in the AUC of 4-hydroxytamoxifen with quercetin. Quercetin improves the AUC of fexofenadine by 55%, C_{max} by 68% and reduces the oral clearance by 37%.[45]

Naringin

Naringin has a variety of pharmacological effects- antioxidant, anticarcinogenic, hypolipidemic. It is a flavonoid glycoside found in apple, grapefruit, and onion. Naringin inhibits CYP3A4, CYP3A1, CYP3A2, P-gp and exerts bio-enhancing activity. Naringin at a dose of 3.3-10 mg/kg body weight increases paclitaxel's plasma concentration and bioavailability. It also enhances the bioavailability of drugs like diltiazem, verapamil, cyclosporine, saquinavir. Naringin inhibits the metabolism of diltiazem and enhances the AUC and C_{max} twice over. A study by Manodeep Chakraborty observed that the poor bioavailability of the cardioprotective phytoconstituent, Resveratrol can be addressed by combining it with naringin. They claimed a notable enhancement in bioavailability, C_{max} with a significant reduction in the clearance rate of the drug combined with naringin.[46]

Gingerol

Gingerol is extracted from the rhizome of Ginger (*Zingiber officinale*) and is reported to produce a bioenhancing action when used in combination with drugs, nutrients and herbal products. Gingerol is shown to have a positive effect on the oral absorption of many co-administered drugs. The absorption enhancing effect is attributed to the ability of gingerol in reducing gastric emptying and GI motility while increasing the blood circulation to the GIT thereby facilitating the increased absorption Gingerol is known to potentiate the bioavailability of rifampicin by 65%, ethionamide by 56%, azithromycin by 78%, ketoconazole by 125%, zidovudine by 105%, and fluorouracil by 110%. Gingerol alone shows bioenhancing effect in the range from 30 to 75% but when combined with piperine enhances bioavailability by10 to 85%. Ginger extract is one of the ingredients of 'Trikatu'. The ginger extracts maintain their bioenhancing activity with and without piperine. So, ginger can be used effectively as a bioenhancer, either alone or in combination with piperine. Studies report the ability of gingerol to potentiate the action of antivirals, antibacterials, and anticarcinogens, by virtue of its bioenhancing effect.[47]

Others

Several other bioenhancers of natural origin have also been reported. These include allicin from garlic (*Allium sativuum*), caraway oil (*Carum carvi*.), Stevia from honey leaf (*Stevia rebaundiana*), Capsaicin from chilli peppers (*Capsicum annum*), Aloe vera gel and whole leaf extract and extract of *Ammannia multiflora*. Allicin is reported to increase the antifungal activity of Amphotericin B against *Candida albicans* and *Aspergillus fumigatus*. Aloe vera extract was found to improve the oral bioavailability of vitamins C and E and is considered promising as a bio-enhancer.[48] Capsaicin is regarded as promising permeation enhancer for transdermal applications of drugs such as indomethacin.[49] Essential oils such as caraway oil have also been used in skin permeation enhancement of drugs.[50] However, there is no information available on the effectiveness of these herbal drugs in enhancing the oral absorption of peptide drugs.

CONCLUSION

The concept of using herbal bioenhancers for improving the intestinal absorption of peptide drugs is exceptionally beneficial as they are safe, effective, easily procured, and economical. The use of herbal bioenhancers helps in decreasing the dose, drug resistance, toxicity, adverse effects, and overall treatment cost. Bioenhancers like piperine, naringin, ginger, glycyrrhizin, and others have great significance either alone or in combination to improve the oral bioavailability of peptide drugs like insulin. Several studies report the ability of herbal bioenhancers to increase the absorption of individual drugs without the need for nanoparticulate carriers. Nevertheless, when it comes to peptides, which require protection from the hostile GI environment before reaching the absorbing membrane, nanocarriers would be optimal in ensuring that peptide drugs reach the target in the intact and potent form. Although there are a few studies that show the efficacy of the combination of piperine with peptide-loaded nanoparticles as described earlier, it is perfectly possible that some of the other herbal bioenhancers, such as gingerol, could be equally effective.

ABBREVIATIONS

GI: Gastrointestinal, **CYP 450:** Cytochrome P450, **EI:** Enzyme inhibitors; **CPP:** Cell-penetrating peptides; **PE:** Permeation enhancers; **ME:** Microemulsion; **P-gp:** P-glycoprotein.

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