

How to Cite:

Wadhwa, S., & Gupta, M. (2022). A review on absorption enhancer and bioenhancer. *International Journal of Health Sciences*, 6(S6), 1854–1866. <https://doi.org/10.53730/ijhs.v6nS6.9908>

A review on absorption enhancer and bioenhancer

Wadhwa S.*

Department of Pharmacy, Lords University Alwar (Raj)

Dr. Mukesh Gupta

Department of Pharmacy, Lords University Alwar (Raj)

Abstract---Poor permeability of orally administered drugs is the major factor limiting the bioavailability of orally administered drugs. The unique barrier properties of the gastro-intestinal membrane, intestinal and presystemic metabolism, intersubject variability also contributors to poor permeability and bioavailability of the drugs. Bioenhancer can benefit the drugs with this problem, especially BCS class III and class IV drugs. Different mechanisms have been established to understand the permeation enhancement effect of different permeation enhancers; their understanding can facilitate the selection of suitable absorption promoters for drugs having specific physicochemical properties. However, certain issues associated with development of absorption promoter technology like lack of in vitro and in vivo correlation of efficacy, reproducibility, and safety. Therefore instead of chemical permeation enhancer herbal bioenhancer is more acceptable due to their better safety profile.

Keywords---bioenhancer, absorption enhancer, bioavailability.

Introduction

Bioavailability of drugs is a complex issue because therapeutic efficacy of the drug depends on it. There are many reasons for low bioavailability of drugs like low aqueous solubility, poor intestinal membrane permeation, degradation of drug in gastric fluids, presystemic intestinal or hepatic metabolism. Various approaches have been used to increase the bioavailability of drugs like microinization, complexation, use of cosolvents/surfactants prodrug approach and microencapsulation. [1-2] For a long time efforts were focused on the processes occurring in the liver and intestine on increasing the solubility and permeability of drugs when addressing the issue of bioavailability. In series of various techniques and approaches, permeation enhancer is also used by various pharmaceutical companies to address this issue. Absorption enhancers are

functional excipients included in formulations to improve the absorption of a pharmacologically active drug. The term absorption enhancer usually refers to an agent whose function is to increase absorption by enhancing membrane permeation, rather than increasing solubility, so such agents are sometimes more specifically termed permeation enhancers. Absorption enhancers have been investigated for at least two decades, particularly in efforts to develop non-injection formulations for peptides, proteins, and other pharmacologically active compounds that have poor membrane permeability. [2-5]

Recently the approaches have been used to increase the bioavailability of drugs by the use of natural compounds. During the past few years a large number of approved new drug applications have originated from the biotechnology industry. Similarly, natural products have contributed nearly half of all small molecules approved in this decade. It may be very helpful if current drug discovery approach of finding 'new entity drugs' is shifted to 'combining existing agents'. Therefore natural product drug discovery based on ethnopharmacology and traditional medicines may also be considered as attractive strategic option. [6] However, based on clues from Ayurvedic literature, a new approach of increasing the bioavailability of drugs including poorly bioavailable drugs had been conceptualized at RRL, Jammu. C.K. Atal, the Director of the institute scrutinized a list of ancient Indian Ayurvedic formulations used in the treatment of a wide range of diseases. He observed that a majority of Ayurvedic formulations contained either Trikatu or else one of the ingredients of Trikatu, namely *Piper longum* (210 formulations out of 370 reviewed) used in a large variety of diseases. Researcher found that mainly piperine act as a bioenhancer for most of the drugs used in experiments and the role of ginger is to regulate intestinal function to facilitate absorption. Based on these findings several other reputed plants were evaluated for bioavailability/bioefficacy or bioenhancing activity. [7] Bioenhancers are molecules, which do not possess drug activity of their own at the dose used but promote and augment the biological activity or bioavailability or the uptake of drugs in combination therapy. This review paper compared the some aspects of the oral permeation enhancer and bioenhancer.

Need of a bioavailability enhancer

It is estimated that globally humans consume about 250 million doses of antibiotics annually and 20 -50% of that use is unnecessary depending on the class of antibiotics. Further, widespread use of antibiotics promotes spread of antibiotic resistance many a times leading to multiple drug resistance. The total amount of drug/antibiotic given for the treatment of any disease is much higher than what is actually required. More ever many therapeutic treatments are also accompanied by loss of essential nutraceuticals in the course of therapy. This is so because all drug/antibiotic given to the patient in a therapy does not reach the target site. This may due to lower absorption, instability, restrictive uptake by microbes, or due to operation of efflux pump. Thus, large portion of drug we apply are wasted and only a miniscule percentage of drug reach at desired site. But even worse part is that the unutilized drug/antibiotic remains as a load in the body and environment. This is then act as a selection pressure, facilitating emergence of drug resistance in parasites which may lead to the failure of antibiotics against resistant infections. Additionally such a situation leads to side

effects, illness and reduction in life expectancy being more acute in older population. One of the ways that has been feasible to reduce drug doses is the occurrence of synergism between different therapeutics agents. However, even in such a situation if both the molecules have antibiotic property, the problem of continued selection pressure on microbes is still likely to continue. Therefore, there the need is for a molecules, which by themselves are not microbicidal but when present with a drug or active molecule, enhance its activity or bioavailability of the drug so the bioenhancer or paracellular permeability enhancer or better choice to reduce time and cost for new drug discovery. Following the use of bioavailability enhancers, the dose of the drug is reduced and risk of drug resistance is minimized. It also reduces the dose-dependent toxicity of the drug, especially of anticancer drugs. [9-10]

Herbal Bioenhancer – An alternative

The term bioavailability enhancer was first coined by Indian scientists C.K. Atal, the Director of the Regional Research laboratory, Jammu, who discovered and scientifically validated Piperine as the world's first bioavailability enhancer in 1979. Natural products especially from plant sources have played an important role in drug development for treatment of communicable diseases. Either the isolated plant biomolecules or its semi synthetic derivatives have provided useful clues in the production of medicines. According to WHO nearly 80% of the world's population relies on herbal medicines as primary health care. Bioenhancers are molecules, which do not possess drug activity of their own at the dose used but promote and augment the biological activity or bioavailability or the uptake of drugs in combination therapy. [10-12]

Advantages of bioenhancer

There are various advantages of using bioenhancer in combination therapy. These are follows –

- Efficacy of drug is increase due to increase in bioavailability.
- Combination of bioenhancer with drug reduces the dosage and dangers of drug resistance can be minimized.
- Adverse drug reaction/side effect and toxicity of drug will be minimized because of reduced dosage. This is especially true of anticancer drugs like Taxol.
- There are ecological benefits too eg. Toxol used to treat ovarian cancer or breast cancer is derived from bark of Pacific yew tree, one of the slowest growing trees in the world. At present to treat one patient, six trees, 25-100 years old need to be felled with ibioenhancers fewer trees will be destroyed.
- They can reduce inter-individual variability as well as intra-individual variability as they increase the bioavailability of drug.
- So another desired effect of an absorption enhancing formulation would be a reduction of intersubject variability. [13-14]

Table 1
List of herbal bioenhancers^[15-30]

S NO	Bioenhancer	Drug/Molecule	Reference
1.	<i>Aloe vera</i>	Vitamin C & E	Vinson JAH 2005
2.	<i>Zingiber officinale</i>	Azithromycin Erythromycin Cephalexin Cephodoxil Amoxicillin Cloxacilin	US Patent No US2003/0170326A1
3.	<i>Carum carvi</i>		US Patent No US20030228381A1
4.	<i>Cuminum cyminum</i>	Erythromycin Cephalexin Amoxicillin Fluconazole Ketoconazole Zidivudine 5-Fluorouracil	US Patent No US007514105B2
5.	Quercetin	diltiazem digoxin, epigallocatechin gallate	Choi and Li, 2005 Dupuy et al., 2003 Anup et al., 2005
6.	Genistein	Paclitaxel	Li X et al., 2007
7.	Naringin	Paclitaxel	Lim SC et al., 2006
8.	Sinomenine	Paeoniflorin	Liu ZQ et al., 2005
9.	Berberine	Digoxin	Qiu W et al., 2009
10.	Glycyrrhetic acid	calcitonin	Imai et al., 1999
11.	Papain	Heparin	Grabovac Vjera et al., 2007
12.	Glycyrrhizin	rifampicin, tetracycline, nalidixic acid, ampicillin vitamin B ₁ and B ₂	Teruko Imai et al., 1999
13.	Niaziridin	rifampicin, ampicillin and nalidixic acid	US Patent No US006858588B2
14.	Lysergol (<i>Rivea corymbosa</i>)	Antibiotics	US Patent No 20070060604A1
15.	<i>Stevia rebaudiana</i>	antibiotics, antidiabetic drugs, antifungal drugs, antiviral drugs, anticancer drugs, cardiovascular drugs, anti-inflammatory, antiarthritic agents, antituberculosis/ antileprosy drugs,	(Gokaraju et al., 2010).
16.	Allicin	Amphotericin B	(Ogita A et al., 2006)
17.	Strawberry extract	Tenofovir Disoproxil	DMD 28:1394–1396, 2000

Table 2
Mechanisms of action of herbal bioenhancers/Piperine ^[31-40]

Mechanisms of action	References
Bioenergetic properties	Reanmongkol et al. (1988), Jamwal and Singh (1993)
Increases gastrointestinal blood supply and reduces	Annamalai and Manavalan

hydrochloric acid secretion	(1990)
Stimulation of γ -glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids	Johri et al. (1992)
Cholagogous effect	Majeed et al. (1996)
Thermogenic and bioenergetics properties	Majeed et al. (1996)
Inhibition of gastric emptying time, gastrointestinal transit	Bajad et al. (2001a)
Inhibition of drug metabolizing enzymes and suppression of first pass metabolism	Atal et al. (1985), Reen et al. (1993), Bhardwaj et al. (2002)
Modifications in GIT epithelial cell membrane permeability	Khajuria et al. (2002)

Table 3
Drug metabolizing enzymes inhibited by bioenhancer/piperine [35-40]

Drug metabolizing enzymes	References
Arylhydrocarbon Hydroxylase (AHH)	Atal et al. (1985), Singh et al. (1986)
Uridine Diphosphate (UDP) Glucuronyl Transferase	Atal et al. (1985), Singh et al. (1986)
Ethylmorphine-N-demethylase	Atal et al. (1985), Singh et al. (1986)
7-ethoxycoumarin-O-deethylase	Atal et al. (1985), Singh et al. (1986)
3-hydroxy-benzo(a)pyrene glucuronidation	Atal et al. (1985), Singh et al. (1986)
UDP-Glucose Dehydrogenase (UDP-GDH)	Reen et al. (1993)
5-lipoxygenase	Stohr et al. (2001)
Cyclooxygenase-1	Stohr et al. (2001)
Cytochrome P450	Atal et al. (1985), Singh et al. (1986), Bhardwaj et al. (2002)

Table 4
Nutraceuticals bioenhanced by piperine^[35]

Class	Examples
Water Soluble Vitamins	Vitamin B1, Vitamin B2, Niacinamide, Vitamin B6, Vitamin B12, Folic acid and Vitamin C
Fat Soluble Vitamins	Vitamin A, β -carotene (provitamin), Vitamin D, Vitamin E and Vitamin K
Amino acids	Lysine, Isoleucine, Leucine, Threonine, Valine, Typtophan, Phenylalanine and Methionine
Minerals	Iodine, Calcium, Iron, Zinc, Copper, Selenium, Magnesium, Potassium and Manganese
Herbal Compounds	Boswellic acid (<i>Boswellia serrata</i>), Ginsenosides (<i>Gingko biloba</i>), Withanaloids (<i>Withania somnifera</i>), Curcuminoides (<i>Curcuma longa</i>) and Pycnogenol (<i>Pinus pinaseter</i>)

Absorption Enhancer or Permeation enhancers

Permeation enhancers increase the permeability of the intestinal epithelium through disruptions of the cellular membrane and/or changes in the structure of the tight junctions between epithelial cells.^[41]

Table 5
Absorption enhancers with mechanisms of action^[42-48]

Absorption enhancer		Mechanism of action
Class	Example	
Fatty acids	Long-chain fatty acids (e.g., sodium caprate, sodium N-[8- (2-hydroxybenzoyl)amino] caprylate (SNAC), 8-(N-2- hydroxy-5-chloro-benzoyl)- amino-caprylic acid (5-CNAC)	Opening of tight junctions Disruption of lipid bilayer packing Formation of membrane permeable complex (IonPair)
	Medium chain glycerides (e.g., Monocaprin)	
	Long chain fatty acid ethers (e.g., palmitoylcarnitine)	
	Omega 3 fatty acid	
	Fatty acids derivatives (e.g., oleic acid, caprylic acid, lauric acid)	Phospholipid acyl-chain disruption
Bile salts	Sodium taurocholate, Sodium taurodeoxycholate, Sodium Taurodihydrofusidate	Disruption of membrane integrity by phospholipids solubilisation and cytolitic effects
	Sodium cholate, sodium deoxycholate, Sodium glycocholate, sodium fusidate Sodium taurodihydrofusidate	Protein denaturation Decreasing mucus viscosity and peptidase activity Solubilizing peptides Forming reverse micelles
Surfactants	Sodium lauryl sulphate, polyoxyethylene, sodium dioctyl sulfosuccinate, laureth-9, polysorbate 20 and 80, PEG-8 laurate, Sorbitan laurate, Glyceryl monolaurate, Quillaja saponins	Extraction of membrane proteins or lipids Solubilization of peptides
Chelating agents	EDTA (ethylene-diamine-tetraacetic acid), EGTA (ethylene-glycol-tetraacetic acid), Citric acid	Modulation of tight junction by complexation with calcium and magnesium.
Salicylates	Sodium salicylate	Increases cell membrane fluidity and complexation with calcium influencing tight junctions
Inclusion complexes	Cyclodextrins and derivatives	Increasing solubility and stability of peptide by enzyme inhibition
Toxins and venom extracts	<i>Zonula occludens</i> toxin	Induction of actin polymerization and tight junction opening by interaction with zonnulin surface receptor
	Melittin	Bilayer micellisation, α -helix channel formation and fusion
Anionic polymers	Poly(acrylic acid) derivatives	Enzyme inhibition and extracellular calcium depletion

Cationic polymers	Chitosan salts and N-trimethyl chitosan chloride	Mucoadhesion and ionic interaction with cell membrane
Swellable polymers	Polycarbophil and chitosan	
Miscellaneous	Azone	Disruption of lipid structure
	Protease inhibitor	Inhibiting protease enzyme

Major issues with Oral permeation enhancer

According to Swenson and Curatolo surfactants can act as permeability enhancers by partitioning into the epithelial cell membrane and disrupting the packing of membrane lipids, forming structural defects that reduce membrane integrity. [49]

Concentration and Time-Dependent Effects

The Absorption enhancer effective in at low conc. but enhancing effect was conc. depended. Several sodium salts of medium chain fatty were studied to enhance the paracellular permeability of hydrophilic compounds but they showed dose-dependent enhancing effect across cell monolayers.

Local Toxicity

The local toxicity of absorption enhancer in the small intestine is one of the main concerns in relation to the use of in pharmaceutical products e.g. mucosal irritation, non-specific damage to intestinal mucosa. At high concentration they may damage or disrupt the cell and such effects are irreversible. Most enhancers, especially surfactants, are toxic at concentrations of 1%.

Change the permeability of cell

Due to their amphiphilic properties surfactants can easily interact with cell membranes, perturb or disrupt the lipid bilayer. This effect depending on applied concentration and treatment time can be reversible but higher concentrations may thin or rupture plasma membranes, damage the microvilli in the apical surface of cells, and lead to leakage of intracellular proteins or cell death. Agents that alter cell membrane permeability in a way that disrupts the normal extracellular-intracellular ion gradients could be cytotoxic, since various cellular functions depend on maintaining transmembrane ion gradients. Medium-chain glyceride/phosphatidylcholine at concentrations of more than 8 mM caused irreversible increases in permeability and altered the morphology of the cell monolayer. [50-52]

pH dependent effect

Chitosan, being a weak base, loses its positive charge in neutral and basic media and thus ineffective as an absorption enhancer at this pH. As compared to other enhancer chitosan has low toxicity but it shows effect in acidic environment. [53-54] Moreover little information available on the long-term safety of compounds that alters intestinal permeability as they can affect cell viability, cell integrity and also

have immunological issues. Bile salts have a high capacity for phospholipid solubilization, and a number of investigators have correlated membrane permeation-enhancing effects with the release of membrane phospholipids and protein. This effect of bile salts could be damaging to the intestinal mucosa. Other disadvantages of absorption enhancers includes ulceration, pin-point membrane 'erosions', which can lead to bacteria, virus entry to the circulatory system from intestine. [55-59]

Recent formulation with absorption enhancer

Recently, sodium caprate has been used as the principal constituent of gastrointestinal permeation enhancement technology (GIPET) by Merrion Pharmaceuticals (Ireland). Sodium caprate was developed as an enteric-coated formulation to enhance the absorption of low molecular weight heparins. Currently, Novo Nordisk (Denmark) is utilizing GIPET™ technology for oral insulin. Isis Pharma (USA) has also developed an enteric-coated formulation of antisense oligonucleotides using C10 fatty acid, which showed enhanced bioavailability in dogs, in pigs, and in preliminary clinical studies. Despite of various safety issues efforts should be made to establish the duration of permeability enhancement, which should be transient to allow fast and complete tissue recovery. [60]

Conclusion

Oral absorption of drug is very important issue specially when the drug is poorly bioavailable, given for long periods and expensive. Poorly bioavailable drugs remain sub-therapeutic because a major portion of a dose never reaches the plasma or exerts its pharmacological effect unless and until very large doses are given which may also lead to serious side effects. Any significant improvement in bioavailability will result in lowering the dose or the dose frequency of that particular drug. Establishing correlations among *in vitro* diffusion experiments and *in vivo* animal studies with actual drug absorption are very difficult. There is a need to understand this relationship. The major concerns associated with absorption enhancers include the association between potency and toxicity. The safety of these intestinal permeability modifying compounds is a crucial aspect in the development of drug delivery systems including enhancers. Cytotoxicity evaluations have been performed mainly *in vitro*, and it seems that the results obtained are not always predictive of *in vivo* toxicity.

Full toxicological assessment of pharmacologically active excipients in preclinical and clinical stages, are mandatory which increase the cost burden in drug formulation process. For example, paracellular enhancers like cytochalasin D have been reported to cause hepatotoxicity. Such events led to safe and selective compounds that fulfill all the needs. So bioenhancers is better choice than paracellular absorption enhancer because they are safe natural compounds. Combining the strengths of the knowledge base of traditional systems such as ayurveda, modern medicine and science will converge to form a real discovery engine that can result in newer, safer, cheaper and effective therapies. Novel biologically active natural products will continue to serve as lead compounds for drug development.

Use of bioenhancer can be considered as new technique/method to increase the bioavailability of drugs in concern to allopathy. Recently Risorine is a formulation developed by Indian Institute of Integrative Medicine, Jammu, and marketed in India in November 2009 in public-private partnership with Cadila Pharmaceutical Ltd, Ahmedabad. Risorine has been approved for marketing by Drug Controller General of India, after successful completion of all the phased clinical trials. It contains rifampicin (200 mg), isoniazid (300 mg), and piperine (10 mg). It has been found to be bioequivalent with commercially available rifampicin preparations. This is due to enhanced uptake of the drug by body cells, and also because the drug remains available in blood for longer durations. Combining piperine with rifampicin decreases the dose of rifampicin from 450 to 200 mg.

The challenge of research and development of herbal bioenhancers is the large scale production. There is always a need to scale up laboratory or pilot technologies for eventual commercialization. Advances in herbal bio-enhancers also provide new challenges for regulatory control. There is an increasing need to have regulations that would account for physicochemical and pharmacokinetic properties of such drug products, which are different from conventional drug products. Therefore extensive research on bioenhancers is needed so that they could be commercialized.

References

1. Hayden Thomas, Shobha Bhattachar, Linda Hitchingham, Philip Zocharski, Maryanne Naath, Narayanan Surendran, Chad L Stoner & Ayman El-Kattan. The road map to oral bioavailability: an industrial perspective. *Expert Opin. Drug Metab. Toxicol.* (2006) 2(4):591-608.
2. Schmid EF and Smith DA. Is pharmaceutical R&D is just a game of chance or can strategy make a difference? *Drug Discov Today* 2004;9:18-26.
3. Swenson ES, Milisen WB, Curatolo W. 1994. Intestinal permeability enhancement: efficacy, acute local toxicity, and reversibility. *Pharm Res* 11:1132-1142.
4. Aungst, B.J., 2000. Intestinal permeation enhancers. *J. Pharm. Sci.* 89, 429-442.
5. Mishra A et al. Oral Absorption Promoters: Opportunities, Issues, and Challenges. *Critical Reviews in Therapeutic Drug Carrier Systems*, 32(5), 363-387 (2015).
6. Patwardhan B, Mashelkar RA. Traditional medicine-inspired approaches to drug discovery: Can Ayurveda show the way forward. *Drug Discovery Today* 2009;14(15/16):804-11.)
7. Johri RK, Zutshi U. An Ayurvedic formulation 'Trikatu' and its constituents. *J Ethnopharmacol* 1992;37:85-91.
8. Khanuja SPS, et al. Nitrile glycoside useful as a bioenhancer of drugs and nutrients, process of its isolation from moringa oleifera. US Patent 6858588. Council of Scientific and Industrial Research, New Delhi, IN. Feb 22, 2005.)
9. Randhawa, Gurpreet Kaur, and Jagdev Singh Kullar. "Bioenhancers from mother nature and their applicability in modern medicine." *International journal of applied and basic medical research* 1.1 (2011): 5-10.

10. Kapil, Randhir S., et al. "Process for preparation of pharmaceutical composition with enhanced activity for treatment of tuberculosis and leprosy." U.S. Patent No. 5,439,891. 8 Aug. 1995.
11. Atal N, Bedi KL. Bioenhancers: Revolutionary concept to market. J-AIM 2010;1(2)96-9.
12. Qazi GN, Bedi KL, Johri RK, Tikoo MK, Tikoo AK, Sharma SC et al. Council of Scientific and Industrial Research. Bioavailability/ Bioefficacy Enhancing Activity of *Cuminum cyminum* and Extracts and Fractions Thereof. US Patent 52873;2004:Mar18.)
13. Atal N, Bedi KL. Bioenhancers: Revolutionary concept to market. J-AIM 2010;1(2)96-99.
14. Singha Ratndeeep et al. Indian Herbal Bioenhancers: A Review: Pharmacognocny. 2009:80-82.
15. Vinson JA et al. Effect of Aloe Vera preparations on the human bioavailability of vitamin C and vitamin E. Phytomedicine2005;12(10):760-765.
16. Qazi G.N., et al. Bioavailability enhancing activity of *Zingiber officinale* and its extracts/fractions thereof. Date of Publication: 11/09/2003. US Patent No , US2003/0170326A1.
17. Qazi G.N., et al. Bioavailability enhancing activity of *Carum carvi* extracts and fractions thereof. Date of Publication: 11/12/2003. US Patent No , US20030228381A1.
18. Qazi G.N., et al. Bioavailability/bioefficacy enhancing activity of *Cuminum cyminum* and extracts and fractions thereof. Date of Publication: 07/04/2009. US Patent No , US007514105B2.
19. J. S. Choi and X. Li. Enhanced diltiazem bioavailability after oral administration of diltiazem with quercetin to rabbits. International Journal of Pharmaceutics 2005;297(1-2):1-8.
20. X. Li and J. S. Choi, "Effect of genistein on the pharmacokinetics of paclitaxel administered orally or intravenously in rats," *International Journal of Pharmaceutics*, 2007;337(1-2):188-193.
21. S. C. Lim and J. S. Choi, "Effects of naringin on the pharmacokinetics of intravenous paclitaxel in rats," *Biopharmaceutics and Drug Disposition*, vol. 27, no. 9, pp. 443-447, 2006.
22. Z. Q. Liu, H. Zhou, L. Liu et al., "Influence of co-administrated sinomenine on pharmacokinetic fate of paeoniflorin in unrestrained conscious rats," *Journal of Ethnopharmacology*, 2005;99(1):61-67
23. Qiu W, et al. Effect of berberine on pharmacokinetics of digoxin after oral administration to rats. Chinese Journal of Chinese Materia Medica. 2011;36(7):918-21.
24. Imai T, Sakai M, Ohtake H, Azuma H, Otagiri M. In vitro and in vivo evaluation of the enhancing activity of glycyrrhizin on the intestinal absorption of drugs. Pharm Res. 1999 Jan;16(1):80-6.
25. Grabovac V, Schmitz T, Föger F, Bernkop-Schnürch A. Papain: an effective permeation enhancer for orally administered low molecular weight heparin. Pharm Res. 2007 May;24(5):1001-6.
26. Khanuja S.P.S., et al. Nitrile glycoside useful as a bioenhancer of drugs and nutrients, process of its isolation from *Moringa oleifera*. Date of Publication: 22/02/2005. United States Patent Number, US006858588B2.
27. Khanuja S.P.S., et al. Antibiotic pharmaceutical composition with lysergol as bioenhancer and method of treatment. Date of Publication: 15/03/2007.

- United States Patent Number, 20070060604A1.
28. Gokaraju, G.R., Gokaraju, R.R., D'souza, C., Frank, E., 2010. Bioavailability/bioefficacy enhancing activity of *Stevia rebaudiana* and extracts and fractions and compounds thereof. Date of Publication: 06/05/2010. US Patent No , US20100112101A1.
 29. Ogita A, Fujita K, Taniguchi M, Tanaka T. combined action of Allicin and Amphotericin B exhibited enhanced antifungal activity against *S. cerevisiae*. *Planta Med* 2006;72:1247-50.
 30. Van Gelder J, et al. Increased absorption of the antiviral ester prodrug tenofovir disoproxil in rat ileum by inhibiting its intestinal metabolism. *Drug Metab Dispos*. 2000;28(12):1394-6.
 31. W. Reanmongkol, W. Janthasoot, W. Wattanatorn, P. Dhumma-Upakorn, and P. Chudapongse, "Effects of piperine on bioenergetic functions of isolated rat liver mitochondria," *Biochemical Pharmacology*, vol. 37, no. 4, pp. 753-757, 1988.
 32. D. S. Jamwal and J. Singh, "Effects of piperine on enzyme activities and bioenergetic functions in isolated rat liver mitochondria and hepatocytes," *Journal of Biochemical Toxicology*, vol. 8, no. 4, pp. 167-174, 1993.
 33. A. R. Annamalai and R. Manavalan, "Effects of "Trikatu" and its individual components and piperine on gastro intestinal tracts: trikatu: a bioavailable enhancer," *Indian Drugs*, vol. 27, no. 12, pp. 595-604, 1990.
 34. R. K. Johri, N. Thusu, A. Khajuria, and U. Zutshi, "Piperine mediated changes in the permeability of rat intestinal epithelial cells. The status of γ -glutamyl transpeptidase activity, uptake of amino acids and lipid peroxidation," *Biochemical Pharmacology*, vol. 43, no. 7, pp. 1401-1407, 1992.
 35. M. Majeed, V. Badmaev, and R. Rajendran, "Use of piperine to increase bioavailability of nutritional compounds," United States Patent Number, US005536506A, 1996.
 36. S. Bajad, K. L. Bedi, A. K. Singla, and R. K. Johri, "Piperine inhibits gastric emptying and gastrointestinal transit in rats and mice," *Planta Medica*, vol. 67, no. 2, pp. 176-179, 2001.
 37. C. K. Atal, R. K. Dubey, and J. Singh, "Biochemical basis of enhanced drug bioavailability by piperine: evidence that piperine is a potent inhibitor of drug metabolism," *Journal of Pharmacology and Experimental Therapeutics*, vol. 232, no. 1, pp. 258-262, 1985.
 38. R. K. Reen, D. S. Jamwal, S. C. Taneja et al., "Impairment of UDP-glucose dehydrogenase and glucuronidation activities in liver and small intestine of rat and guinea pig *in vitro* by piperine," *Biochemical Pharmacology*, vol. 46, no. 2, pp. 229-238, 1993.
 39. R. K. Bhardwaj, H. Glaeser, L. Becquemont, U. Klotz, S. K. Gupta, and M. F. Fromm, "Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4," *Journal of Pharmacology and Experimental Therapeutics*, vol. 302, no. 2, pp. 645-650, 2002.
 40. A. Khajuria, N. Thusu, and U. Zutshi, "Piperine modulates permeability characteristics of intestine by inducing alterations in membrane dynamics: influence on brush border membrane fluidity, ultrastructure and enzyme kinetics," *Phytomedicine*, vol. 9, no. 3, pp. 224-231, 2002.
 41. Renukuntla J, Vadlapudi AD, Patel A, Boddu SH, Mitra AK. 2013. Approaches for enhancing oral bioavailability of peptides and proteins. *Int J*

- Pharm 447:75-93.
42. Hochman J, Artursson P. Mechanisms of absorption enhancement and tight junction regulation. *J Control Release*. 1994;29(3):253-67.
 43. Kathryn Whitehead, Natalie Karr, Samir Mitragotri. Discovery of synergistic permeation enhancers for oral drug delivery. *Journal of Controlled Release* 128 (2008) 128-133.
 44. Salama NN, Eddington ND, Fasano A. Tight junction modulation and its relationship to drug delivery. *Adv Drug Deliv Rev*. 2006 Apr 20;58(1):15-28.
 45. Swenson ES, Milisen WB, Curatolo W. Intestinal permeability enhancement: structure activity and structure-toxicity relationships for phenoxypropoxyethylene surfactant permeability enhancers. *Pharm Res*. 1994 Oct;11(10):1501-4.
 46. Bohets H, Annaert P, Mannens G, Anciaux K, Verboven P, Meuldermans W, Lavrijsen K. Strategies for absorption screening in drug discovery and development. *Curr Top Med Chem*. 2001;1(5):367-83.
 47. Uchiyama T, et al. Enhanced permeability of insulin across the rat intestinal membrane by various absorption enhancers: their intestinal mucosal toxicity and absorption-enhancing mechanism of n-lauryl-beta-D-maltopyranoside. *J Pharm Pharmacol*. 1999 Nov;51(11):1241-50.
 48. Bowe CL, et al. Design of compounds that increase the absorption of polar molecules. *Proc Natl Acad Sci USA*. 1997;94(22):12218-23.
 49. Swenson ES, Milisen WB, Curatolo W. Intestinal permeability enhancement: efficacy, acute local toxicity, and reversibility. *Pharm Res*. 1994 Aug;11(8):1132-42.
 50. Anderberg EK, Nyström C, Artursson P. 1992. Epithelial transport of drugs in cell culture. VII: Effects of pharmaceutical surfactant excipients and bile acids on transepithelial permeability in monolayers of human intestinal epithelial(Caco-2) cells. *J Pharm Sci* 81:879-887.
 51. Hamid KA, Katsumi H, Sakane T, Yamamoto A. 2009. The effects of common solubilizing agents on the intestinal membrane barrier functions and membrane toxicity in rats. *Int J Pharm* 379:100-108.
 52. Sakai M, Imai T, Ohtake H, Azuma H, Otagiri M. 1998. Effects of absorption enhancers on cytoskeletal actin filaments in Caco-2 cell monolayers. *Life Sci* 63:45-54.
 53. Kotze, A.F., Luessen, H.L., De Boer, A.G., Verhoef, J.C., Junginger, H.E., 1998a. Chitosan for enhanced intestinal permeability: Prospects for derivatives soluble in neutral and basic environments. *Eur. J. Pharm. Sci.* 7, 145-151.
 54. Kotze, A.F., Luessen, H.L., De Leeuw, B.J., De Boer, A.G., Verhoef, J.C., Junginger, H.E., 1998b. Comparison of the effect of different chitosan salts and *N*-trimethyl chitosan chloride on the permeability of intestinal cells (Caco-2). *J. Contr. Rel.* 51, 35-46.
 55. Thanou, M., Verhoef, J.C., Romeijn, S.G., Nagelkerke, J.F., Merkus, F.W.H.M., Junginger, H.E., 1999. Effects of *N*-trimethyl chitosan chloride, a novel absorption enhancer, on Caco-2 intestinal epithelia and the ciliary beat frequency of chicken embryo trachea. *Int. J. Pharm.* 185, 73-82.
 56. C. Jonker, J.H. Hamman, A.F. Kotze. Intestinal paracellular permeation enhancement with quaternised chitosan: in situ and in vitro evaluation. *International Journal of Pharmaceutics* 238 (2002) 205-213.)
 57. Ana Polache. Intestinal Absorption Enhancement Via the Paracellular Route

- by Fatty Acids, Chitosans and Others: A Target for Drug Delivery. *Current Drug Delivery*, 2005, 2, 9-22.)
58. María José Cano-Cebrián, Teodoro Zornoza, Luis Granero and Ana Polache. Intestinal Absorption Enhancement *Via* the Paracellular Route by Fatty Acids, Chitosans and Others: A Target for Drug Delivery. *Current Drug Delivery*, 2005, 2, 9-22.)
 59. Anilkumar P, et al. A rationalized description on study of intestinal barrier, drug permeability and permeation enhancers. *Journal of Global Trends in Pharmaceutical Sciences*, 2011, 2(4)431-49.
 60. Misra A at al. Oral Absorption Promoters: Opportunities, Issues, and Challenges. *Critical Reviews in Therapeutic Drug Carrier Systems*, 32(5), 363–387 (2015).
 61. Suryasa, I. W., Rodríguez-Gómez, M., & Koldoris, T. (2021). Get vaccinated when it is your turn and follow the local guidelines. *International Journal of Health Sciences*, 5(3), x-xv. <https://doi.org/10.53730/ijhs.v5n3.2938>
 62. Suryasa, I. W., Rodríguez-Gómez, M., & Koldoris, T. (2021). Health and treatment of diabetes mellitus. *International Journal of Health Sciences*, 5(1), i-v. <https://doi.org/10.53730/ijhs.v5n1.2864>
 63. Amir, . F., Suhron, M., & Sulaihah, S. (2021). Family care model development in treating schizophrenia patients that have self-deficit nursing based system: Structural equation modeling analysis. *International Journal of Health & Medical Sciences*, 5(1), 7-14. <https://doi.org/10.21744/ijhms.v5n1.1808>