REVIEW

ISSN (O): 2349-5332
CODEN: IRJPHY

A REVIEW ON HERBAL BIOENHANCERS

Tanmay Mohanta*, Saumendu Deb Roy

Mata Gujri College of Pharmacy; Kishanganj, Bihar

Submitted on: 15.02.2023; **Revised on:** 05.03.2023; **Accepted on:** 22.03.2023

ABSTRACT:

Bioenhancer is a revolutionary prospect for us. It is a latex of Indian traditional Charaka, Sushruta and other medicinal system in tradition. Lipid solubility and molecular size is most important problem for maintaining the bioavailability of a drug as well as effect of toxic drug, cost of drugsis another problem which can be managed by enhancing bioavailability. To overcome these problems, herbal compounds like silymarin, naringenin, curcumin can be used to enhance the bioavailability. In recent era there are various novel drug delivery system focused on enhancing the bioavailability. Liposomal formulation, nano materials, transferosome also used to enhance the bioavailability. But there are some practical drawbacks regarding large-scale production of these products.

KEYWORDS: Bioenhancer, lipid solubility, charaka, sushruta, bioavailability, transferosome.

Corresponding address: T. Mohanta
Mata Gujri University, Kishanganj

Indian Research Journal of Pharmacy and Science; 34(2023)2825-2831;
Journal Home Page: https://www.irjps.in

INTRODUCTION:

From ancient times to present era Ayurveda has a great role in discovery of active phytoconstituents. It has given a big helping hand to discover the new drug entity [1]. Bioenhancersare such great agents which does not give any synergism but trigger and increase the bioavailibity[2]. Lipid solubility is most important thing for bio enhancing. Some herbal drugs and plants do not easily solubilize in fat which is the reason behind their low bioavailability[3]. So, there is a great and beautiful relationship between novel drug delivery system and bioenhancer for bioavailability of a product. For some drugs especiallywater-soluble, for their inability to cross the lipid membrane of intestine, are delivered throughvarious newer drug delivery systems; like in the form of liposome, microsphere, transferosome, niosome to cross the fatty layer [4].

Importance of Bioenhancers:

Intestinal epithelial layer makes huge problem to pass the drug from lumen of gut to systemic circulation to show the drugs biological activity [5,6]. Size of drug molecule must need below 0.4mm, as at this size p-glycoprotein gives great opportunity to pass the barrier and transfer the drug into systemic circulation [7,8]. According to C. K. Atal, a pioneer of pharmacognosy, whoscrutinized a list of formulation of ancient Indian ayurveda "Trikatu" containing black pepper (*piper nigrum*), long pepper (*P. longum*) and ginger (*Zingiber officinalate*), where pepper has the most important constituentwhich shows the enhanced bioavailability of various drugs [9.10].

Procedure of enhancement of bioavailability for extravascular route drugs:

Bioavailability enhancers lowers the HCl secretion and uphold the GI blood supply, stopping the GI transit, emptying time of gastric juice, intestinal motility, suffocate the first pass metabolism and working of metabolizing activity as well as increase the loading of amino acid by triggering of gamma glutamyl transpeptidase [11,12,13,14,15,16,17].

Absorption enhancer, prodrug, dosage form and other pharmaceutical approaches like p- glycolprotein inhibitors can take great responsibility for enhancement of bioavailability. Calcium chelators like ethylene glycol tetra acetic acid and ethylene diamine tetra acetic acid increase the absorption by decreasing the extracellular calcium concentration [18].

In prodrug strategy, various derivatives of ampiciline like pivampiciline, bacampiciline which denotes as a prodrug of ampiciline gives huge response in bioavailability enhancement[19].

Specially liposomal drug delivery system, microsphere, nano-sphereetc shows the enhanced bioavailability [20,21,22,23]. P- glycoprotein inhibitor trigger the metabolism, absorption, distribution and excretion and as well as it has huge effect on what the body does to drug [24].

Natural components for enhancing bioavailability:

(i) Sinomerine: Paeoniflorin is one of the most important components for inflammation and arthritis treatment. But the main problem is that it has very low bioavailability. Here sinomerine which is extracted from *Sinomeriniumactum*, plays a very important role on co-administration with paeniflorin, which gives the

increasing activity of paeniflorin and it is 12 times more effective in rats [25,26,27].

(ii) Aloe vera: Vitamins are very important for human body and *aloe vera* increases the bioavailability of vit C and vit E[28].

(iii) *Allium Sativum*: *Saccharomyces cerevisiae* is a very common yeast. Allicin which is obtained from *Allium Sativum* increases the activity of Amphotericine B and helps to fight*S. cerevisiae* [29].

(iv) Quercetein: It contains antioxidant, anti tumour, antiviral property. It has increased the bioavailability, blood level and efficiency of drugs like digoxin, diltiazem etc [30,31,32,33.34].

(v) Genistein: One of the most important and common phyto-estrogen is genistein[35]. Genistein gives a huge response if we use it with paclitaxel and it inhibit the p-glycoprotein, BCRP, MRP2 [36,37]. Genistein decreases the the total plasma clearence and increase the area under curve.

(vi) Naringin: Naringin is a CYP3A1/2 and p-glycoprotein inhibiting compound. It is present in grapes and gives a huge effect as lipid lowering , antioxidant and anti-carcinogen. If we use extravascular naringenin 30min before IV administration of paclitaxal, it increases AUC near about 40.8% and 49.1% for a doses of 3.3 and 10mg/kg [38,39]

(vii) *Zingiber officinalis*: Nearabout 10mg/kg of body weight is used as bioenhancer. It maintains the intestinialmotility and gastric mucosa. It helps to increase the bioavaility of azithromycine, erythromycin, cephalosporin like 85%, 11%, 85% etc [40].

Various liposomal formulation, nanoparticles transferosome for bioenhancer

Table1: Liposomal Formulations[41]

Formulation	Active ingredient	Application	Biological activity	Method of preparation	Percent entrapment efficiency	Route of administration
Quercetin Liposome	Quercetine	Reduced dose, enhanced penetration in blood brainbarrier	Anti-oxidant Anti-cancer	Reverse evaporation technique	60%	intranasal
Liposome encapsulated Silymarin	Silymerine	Improve bioavailability	Hepatoprotective	Reverse evaporation technique	69.22依0.6%	buccal
Ampelopsin liposome	Ampe-lopsin	increase efficiency	Anti-cancer	Film ultrasound method	62.30%	Invitro
Paclitaxel liposome	Paclitaxel	High entrapment efficiency and Ph sensitive	Anti-cancer	Thin film hydration method	94%	Invitro
Curcumin liposome	Curcumin	Long circulation with high entrapment effeciency	Anti-cancer	Ethanol injection method	88.27依2.16%	Invitro

Table 2: Nanoparticle Formulations [41]

Formulation	Active ingredient	Application	Biological activity	Method of preparation	Percent entrapment efficiency	Route of administration
Triptolide Nanoparticles	Triptolide	Enhance the penetration of drug through stratum corneum by increased hydration	Anti-inflam-matory	Emulsi-fication ultrasound		Topical
Nanoparticle of Cuscuta chinensis	Flavonoids and Lignans	Improve water solubility	Hepato-protective and anti-oxidant activity	Nano-suspension Method	90%	oral
Artemisinin nanocapsules	Artemisinin	Sustained drug release	Anti-cancer	Self assembly procedure	90-93%	In-vitro
Radix salvia miltiorrhiza nanoparticles	Radix salvia	Improve the bio-availability	Coronary heart diseases, angina pectoris and myocardial infraction	Spray drying technique	96.68%	In-vitro
Taxol loaded nanoparticles	Taxol	Improve the bioavailability and sustained drug release	Anti-cancer	Emulsion solvent evaporation method ionic gelation method.	99.44%	In-vitro
Naringenin loaded nanoparticles	Naringenin	Improve the release of NAR and improv its solubility	Hepato-protective	Nano-precipitation method		oral

Table 3: Transferosome Formulations [41]

Formulation	Active ingredient	Application	Biological activity	Droplet size	Route of administration
Capsaisin transferosome	Capsaisin	Increase skin penetration	Analgesic	150.6nm	Topical
Colchisin transferosome	Colchisin	Increase skin penetration	Antigout		Invitro
Vincristin transferosome	Vincristin	Increase entrapment efficiency and skin penetration	Anticancer	120nm	Invitro

Merits and demerits:

Lipids are not easily soluble and their molecular size is a big problem for bioavailability. So, bioavailability enhancer can enhance the bioactivity and reduce the molecular size problem and increase the lipid solubility [41]

Overall bioenhancer is a very good project for us but it is not successful in each and every places. If we keep our eyes open in research and development, we can observe some drawbacks of it. It is a largescale project where we need large scale laboratory and facilities. As well as it musttake care of the protection of the incorporated drugs,duringits journey with blood. [42].

Application:

Piperine is used as a bioenhancer and nutritional additives of vitamins. Curcumin is used as a co-enzyme. Bio enhancers can reduce the dosage and cost of expensive medication while making treatment safer. Bioenhancer increases the poor bioavailability of drug by improving the molecular size and lipid solubility [43].

Conclusion:

Bioenhancer is a revolutionary prospect for us. lipid solubility, molecular sizes are improved by the bioenhancers. It is a large scale production product and we cannot make it in small quantity. Bioenhancers are used in novel drug delivery system. There are many herbal drugs like silymarin, curcumin etc which are used as bio enhancers, which can increase the activity of drug molecules.

References:

1. Patwardhan B, Mashelkar RA. Traditional medicine-inspired approaches to drug discovery and development: can Ayurveda show a way forward? Drug Discov Today 2009; 14: 804-811.
2. Brahmankar DB, Jaiswal S. Biopharmaceutics and Pharmacokinetics: A Treatise.March1995; (1): 24-26.
3. Manach C, Scalbert A, Morand C. Polyphenols: food sources and bioavailability. Am J Clin Nutr2004; 79: 727-747.
4. Uchegbu IF, Vyas SP. Non ionicsurfactant based vesicles (Niosomes) in drug delivery. Int J Pharma 1998; 172: 33-70.
5. Hayton WL. Low dose ethanol in the treatment of ethylene glycol poisoning. J Vet Pharmacl Ther 1985; 8: 254-262.
6. Veiga F, Fernandes C, Teixeira F. Oral bioavailability and hypoglycaemic activity of tolbutamide/cyclodextrin inclusion complexes. Int J Pharm 2000; 202: 165-171.
7. Schinkel AH, Jonker JW. Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview. Adv Drug Del Rev 2003; 55: 3-29.
8. Juliano RL, Ling L. P-glycoprotein, a type of ATPase and an energy dependent trans membrane drug efflux pump, Biochem. Biophys Acta 1976; 555: 152-16
9. Johri RK, Zutshi U. An Ayurvedic formulation 'Trikatu' and its constituents. J Ethnopharmacol1992; 37: 85-91.
10. Shaikh J, Ankola DD, Beniwal V, Singh D, Kumar MN. Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer. Eur J Pharm Sci 2009; 37: 223-230
11. Annamalai AR, Manavalan R. Effects of Trikatuand its individual components and piperine on gastrointerstinal tracts: Trikatua

bioavailable enhancer. Ind Drugs 1989; 27(12): 595-604.

12. Bajad S, Bedi KS, Singla AK, Johri RK. Piperine inhibits gastric emptying and gastrointestinal transit in rats and mice. Planta Med 2001; 67: 176-179.

13. Majeed M, Badmaev V, Rajendran R. Use of piperine to increase the bioavailability of nutritional compounds. United States Patent, Number 5536506. 1995.

14. Khajuria A, Thusu N, Zutshi U. Piperine modulates permeability characteristics of intestine by inducing alterations in membrane dynamics: influence on brush border membrane fluidity, ultrastructure and enzyme kinetics. Phytomed2002; 9: 224-231.

15. Reanmongkol W, Janthasoot W, Wattanatorn W, Upakorn PD, Chudapongse P. Effects of Piperine on bioenergetics functions of isolated rat liver mitochondria. BiochemPharmacol1988; 37: 753-757

16. Atal CK, Dubey RK, Singh J. Biochemical basis of enhanced drug bioavailability by piperine: evidence that piperine is a potent inhibitor of drug metabolism. J Pharmacol Exp Therap1985; 232: 258-262.

17. Johri RK, Thusu N, Khajuria A, Zutshi U. Piperine mediated changes in the permeability of rat intestinal epithelial cells: Status of gamma glutamyl transpeptidase activity, uptake of amino acids and lipid peroxidation. BiochemPharmacol1992; 43: 1401-1407.

18. Schipper NGM, Olsson S, Hoogstraate JA, Boer AG, Varum KM, Artursson P. Chitosan an absorption enhancers for poorly absorbable drugs: influence of molecular weight and degree of acetylation on derug transport acroos human intestinal epithelial(Caco-2) cells. Pharm Res 1997; 113: 1686-1692

19. Buur A, Bundgaard H, Falch E. Prodrugs of 5-fluorouracil. VII. Hydrolysis kinetics and physicochemical properties of N-ethoxyand N-phenoxycarbonyloxymethyl derivatives of 5-fluorouracil. Acta Pharm Suec1986; 23: 205-216.

20. Patel HM, Ryman BE. The gastrointestinal absorption of liposomally entrapped insulin in normal rats. Biochem Soc Trans 1977; 5: 1054-1055.

21. Engel RH, Riggi SJ, Fahrenbach MJ. Insulin: intestinal absorption as oil-in-water-in-water emulsions. Nature 1968; 219: 856-857.

22. Liversidge GG, Cundy KC. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. Int J Pharm 1995; 125: 91-97.

23. Veiga F, Fernandes C, Teixeira F. Oral bioavailability and hypoglycaemic activity of tolbutamide/cyclodextrin inclusion complexes. Int J Pharm 2000; 202: 165-171

24. Varma MV, Ashokraj Y, Dey CS, Panchagnula R. P-glycoprotein inhibitors and their screening: a perspective from bioavailability enhancement. Pharmacol Res 2003; 48: 347-359

25. Takeda S, Isono T, Wakui Y, Matsuzaki Y, Sasaki H, Amagaya S, et al. Absorption and excretion of paeoniflorin in rats. J Pharm Pharmacol1995; 47: 1036-1040.

26. Liu ZQ, Zhou H, Liu L, Jiang ZH, Wong YF, et al. Influence of coadministratedsinomenine on pharmacokinetic fate of paeoniflorin in unrestrained conscious rats. J Ethnopharmacol2005; 13: 61-67.

27. Chan K , Liu XZ, Jiang ZH, Zhou H, Wong YF, Xu HX, et al. The effects of sinomenine on intestinal absorption of paeoniflorin by the everted rat gut sac model. J Ethnopharmacol2006; 20: 425-432.

28. Vinson JA, Kharrat HA, Andreoli L. Effect of Aloe vera preparations on the human bioavailability ofvitami C and E. PhytotherPhytopharmacol2005; 12: 760-765

29. Ogita A, Fujita K, Taniguchi M, Tanaka T. Enhancement of the fungicidal activity of amphotericin B by allicin, an allyl-sulfur compound from garlic, against the yeast

Saccharomyces cerevisiae as a model system. Planta Med 2006; 72: 1247-1250.

30. Nijveldt RJ, Nood EV, van Hoorn DEC, Boelens PG, Norren K, van Leeuwen PAM. Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr2001; 74: 418-425.

31. Hoi JS, Li X. Enhanced diltiazem bioavailability after oral administration of diltiazem with quercetin to rabbits. Int J Pharm 2005; 297: 1-8.

32. Dupuy J, Larrieu G, Sutra JF, Lespine A, Alvinerie M. Enhancement of moxidectin bioavailability in lamb by a natural flavonoid: quercetin. Vet Parasitol2003; 112: 337-347.

33. Wang YH, Chao PD, Hsiu SL, Wen KC, Hou YC. Lethal quercetindigoxin interaction in pigs. Life Sci 2004; 74: 1191-1197.

34. Anup K, Sonia G, Swati K, Shrirang N, Waheed R, Vadim I, et al.The studies on bioenhancer effect of red onions and other nutrients on the absorption of epigallocatechin gallate from green tea extract in human volunteers. Boston: 2nd International Conference on Tumor Progression & Therapeutic Resistance Proceedings; 2005, p. 89. Pichard LG, Gillet G, Fabre

35. Kurzer M, Xu X. Dietary phytoestrogens. Annu Rev Nutr2003; 17: 353-381.

36. Sparreboom A, van Asperen J, Mayer U, Schinkel AH, Smit JW, Meijer DK, et al. Limited oral bioavailability and active epithelial excretion of paclitaxel (taxol) caused by P-glycoprotein in the intestine. Proc Natl Acad Sci 1997; 4: 2031-2035.

37. Doyle LA, Ross DD. Multidrug resistance mediated by the breast cancer resistance protein BCRP (ABCG2). J Oncogene 2003; 22: 7340-7358.

38. Lim SC, Choi JS. Effects of naringin on the pharmacokinetics of intravenous Paclitaxel in rats. Biopharm Drug Dispos2006; 27: 443-447.

39. Cheng SS, Fu SX, Li YS, Wang NC. The pharmacology of sinomenine I: the analgesic and anti-phlogistic actions and acute toxicity. Acta Pharmacol Sin 1964; 4: 177-180.

40. Qazi GN, Tikoo GL, Gupta AK, Ganjoo SK, Gupta DK, Jaggi BS, et al, inventor. Bioavailability enhancing activity of Zingiber officinale and its extracts/fractions thereof. European Patent Number EP 1465646. 2002. Khanuja SPS, Arya JS, Sri

41. Kritika Kesarwani, Rajiv Gupta, Bioavailability enhancers of herbal origin: An overview, Asian Pac J Trop Biomed 2013; 3(4): 253-266

42. Wagner V, Dullaart A, Bock A-K, Zweck A. The emerging nanomedicine landscape. Nat Biotech 2006; 24(10): 1211-1217.

43. Kesarwani K, Gupta R and Mukerjee. Bioavailabity enhancers or herbal origin: A review.Asian Pacific Journal Trop. Biomedichemistry, March 2003:253-266.

CONFLICT OF INTEREST REPORTED: NIL; SOURCE OF FUNDING: NONE REPORTED