Review Article

An appraisal of the bioavailability enhancers in Ayurveda in the light of recent pharmacological advances

Satyapal Singh, J. S. Tripathi, N. P. Rai

Department of Kayachikitsa, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Abstract

The concept of bioavailability enhancer is new to the modern system of medicine. Basically, this concept originated in Ayurveda and being used in this system of medicine since centuries. Bio-enhancers augment the bioavailability or biological activity of drugs when co-administered with principal drug at low doses. Ayurveda is using several drugs such as *Piper longum* Linn., *Zingiber officinale* Rosc., and *Glycyrhhiza glabra* Linn. as bio-enhancers and different methods for bio-enhancing since centuries. The bio-enhancement leads to reduction in therapeutic dose of principal drug, thus reducing the possibilities of toxicity and side effects of drug, potentiating the efficacy, reducing the resistance, decreasing the requirement of raw material for drug manufacture, and ultimately benefitting to the world economy by reducing the treatment cost. This review article attempts to consolidate different drugs as well as methods being used traditionally for enhancing bioavailability in Ayurvedic system of medicine and to discuss their possible mechanism of action. Authentic subject material has been reviewed from different Ayurvedic texts and from different related research and review articles. Thus, it is a humble effort to explore the different aspects of bio-enhancers including therapeutic techniques such as *Shodhana*, the drugs such as *Pippali,* and properties such as *Yogavahi* and *Rasayana,* which have been described in Ayurveda along with their mechanism of action and uses wherever available.

Keywords: Ayurveda, bioavailability, bio-enhancer, herbal bio-enhancers, piperine, *Yogavahi*

Introduction

There is an increasing interest and medical need for the improvement of bioavailability of a large number of drugs. With rapid advances in drug design technologies, many drugs have dramatically been introduced. Therefore, improving oral drug absorption and bioavailability of such drugs has become an important issue within the pharmaceutical industries.

Most of the plant constituents, specifically phenolics are water soluble, and so the major problem for less bioavailability is their inability to cross the lipid membranes of the intestine. Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogeneous system, and it is one of the important parameters to achieve the desired concentration of drug in systemic circulation for a pharmacological response. Poorly water-soluble drugs after oral administration often require high doses to reach therapeutic plasma concentrations. The bioavailability of an orally administered drug depends on its solubility in aqueous media over different pH ranges. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water-soluble compounds.

Access this article online

Quick Response Code:

Website: www.ayujournal.org

DOI: 10.4103/ayu.AYU_11_15

At present, several methods for enhancing the intestinal absorption have been in use, these methods include the use of absorption enhancers, pro-drugs, P-glycoprotein (P-gp) inhibitors, and permeability-enhancing dosage forms such as liposomes and emulsions. Recently, the application of P-gp inhibitors in improving per-oral drug delivery has gained a special interest.[1]

Classification of Ayurvedic concepts related with bio-enhancing effect

The concept of bio-enhancers or bio-potentiators is new to the modern science. In contrast to this, many drugs as bioavailability enhancers are being used in Ayurveda since time immemorial. Therefore, basically, this concept is originated

Address for correspondence: Dr. Satyapal Singh, Senior Resident and Research Scholar, Department of Kayachikitsa, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221 005, Uttar Pradesh, India.
E-mail: spmairti@gmail.com

How to cite this article: Singh S, Tripathi JS, Rai NP. An appraisal of the bioavailability enhancers in Ayurveda in the light of recent pharmacological advances. AYU 2016;37:3-10.

in Ayurveda. For the first time, it was reported by Bose in 1929,[2,3] who described the increase in the anti-asthmatic effects of *Vasaka* (*Adhatoda vasica* Nees.) leaves by the addition of long pepper (*Piper longum* Linn.) to it. The term bioavailability enhancer was first coined by Indian Scientists at the Regional Research Laboratory, Jammu (RRL, now known as the Indian Institute of Integrative Medicine), who discovered and scientifically validated piperine as the world's first bioavailability enhancer in 1979. The usage of Ayurvedic preparation "*Trikatu,*" especially during the period between the 7th century B.C. and the 6th century A.D. provided more weightage to the practice of bio-enhancing. *Trikatu* refers to a combination of three acrid drugs, *Maricha* (*Piper nigrum* Linn.), *Pippali* (*P. longum*), and *Shunthi* (*Zingiber officinale* Rosc.), having "piperine" as the principal phytoconstituent, which enhances the bioavailability of drugs, nutrients, vitamins, etc.[2]

The concepts and methods like *Yogavahi*, *Anupana, Bhaishajya Kala, Bhavana* (trituration), *Rasayana, Yoga* (formulations) and *Kalpanas* (various dosage forms), concept of *Purana Aushadhies* (old drugs), concept of action-augmenting drugs, and penetration enhancers of bio-enhancing are being used since time immemorial in Ayurveda. In addition *Samshodhana* (bio-purification) can also be considered for this concept.

Yogavahi

The concept of *Yogavahi* for enhancing bioavailability is being used in Ayurveda since time immemorial.[4,5] A very common example of *Yogavahi* in Ayurveda includes *Pippali* (*P. longum*) and *Maricha* (*P. nigrum*), which contain an important active compound named "piperine" (1-piperonyl piperidine) which is responsible for bio-enhancing effect. Piperine is a well-established bio-enhancer used for potentiating the bioavailability and efficacy of many drugs including vasicine, sparteine, sulfadiazine, rifampicin, phenytoin, and propranolol.[6-8] It has been found that piperine's bioavailability-enhancing property may be attributed to increased absorption, which may be due to alteration in membrane lipid dynamics and change in the conformation of enzymes in the intestine. Piperine has been demonstrated to increase the serum levels and lengthen the serum half-lives of some nutritional substances, such as coenzyme Q10 and beta-carotene. On the basis of traditional use, honey is considered the best *Yogavahi* by many authors in Ayurveda.[9] Other common examples of *Yogavahi* include *Ghrita*, *Swarna* (gold) preparation, *Guggulu* preparation, and *Bhasmas*.

Recent scientific evidences for bio-enhancing effect of *Pippali* (piperine)

Piperine, an active principle of *Pippali,* has been extensively studied for its bio-enhancing effect. Piperine has the following proposed mechanisms of action.[10]

- Inhibition of drug metabolism pathways: It acts on enzymes that are responsible for drug metabolism and degradation. Piperine inhibits human P-gp and cytochrome P450 3A4 (CYP3A4).[11] Both these proteins contribute to a major extent to the first-pass elimination of many drugs. It inhibits mainly P-gp class and CYP3A4 (cytochrome P-450). Some of the other enzymes of cytochrome P-450 class inhibited or induced include CYP1A1, CYP1B1, CYP1B2, CYP2E1, and CYP3A4. P-gp is the major efflux pump of cell, mainly important in case of antimalarial or antineoplastics. This pump throws out the ingested drug. Apart from these, piperine also inhibits other enzymes, namely, Aryl hydrocarbon hydroxylase (microsomal enzyme system), ethyl morphine-N demethylase, 7-ethoxycoumarin-O-de-ethylase, 3-hydroxy-benzo (a) pyreneglucuronidase, uridine di phosphate glucose dehydrogenase (UDP), UDP-glucuronyl transferase 5-lipoxegenase, and cyclo-oxygenase-I[12-14]
- Inhibition of glucuronic acid: It interferes with the extent of glucuronidation in the gut. Mainly, it lowers the endogenous UDP-glucuronic acid content and also inhibits the transferase activity. In several experimental studies on rats, piperine has been demonstrated as a strong inhibitor of UDP-glucuronyl-transferase[13]
- Extent of absorption: It increases the absorption of drug molecule in the gastrointestinal region because it vasodilates the tissues that results in a greater extent of perfusion in the area[15]
- Stimulation of gamma glutamyltranspeptidase (GGT): GGT is an important amino acid transporter found in the gut region, its stimulation enhances the uptake of amino acids which ultimately enhance the absorption of drugs that conjugates with amino acid[16]
- Miscellaneous: It is assumed that piperine acts as a receptor for certain molecules or enhances the sensitivity of receptors. It also modulates cell transduction pathways, hence decreasing the efflux signals. Modulation of dynamics of cell barrier or blood–brain barrier ultimately ends in the enhancement of transportation of drugs.[17]

Some of the scientifically documented drugs, which are affected by "piperine" co-administration are cited in Table 1.[7,18-26]

Anupana

The administration of medicament/drug with or after the core drug is known as *Anupana*. Acharya Charaka had mentioned that *Anupana* taken in a proper manner helps in the proper digestion and absorption of drug and food material and ultimately leading to an increased bioavailability.[27] Use of *Anupana* according to *Dosha* is also narrated in classics [Table 2].[28,29]

The various types of *Anupana* described in Ayurveda are classified on the basis of *Dosha* predominance, nature of disease, and administered drugs. The concept of *Anupana* basically comes into existence due to the low efficiency of drugs. The co-administration of *Anupana* may increase the bioavailability and efficiency of drugs.

Table 1: Some scientifically documented drugs which are affected by co-administration of "piperine"

Name of drug	Clinical model	Experimental assumption of action
Phenytoin/carbamazepine	Human subjects immunoassay	At a high dose, piperine diminishes the elimination or metabolism that results in higher amount available. It helps in the management of epilepsy rapidly at lower doses
Pentobarbitone	Pentobarbitone-induced hypnosis in rats	Significantly potentiate the sleeping time in comparison with the control group due to inhibition of liver microsomal enzyme system
Curcuminoids	Rats and human beings	Curcumin gets rapidly metabolized by liver and gut enzymes. Piperine increases the bioavailability by 200%. The effect is due to the inhibition of hepatic and intestinal glucuronidation
EGCG (green tea)	In albino mice	This polyphenol showed chemopreventive activity in animal models, but with piperine, the activity of drug has increased by 1.3 times when compared to normal treatment group. Mechanism that works behind this concept is inhibition of glucuronidation and gastro-intestinal transit time
Coenzyme Q10	Double-blind cross-over	Supplementation of piperine with coenzyme Q10 for a long time or at a high dose only can increase the bioavailability. It is assumed that piperine follows nonspecific thermogenic or bioenergetics properties for augmentation
Nimesulide, diclofenac sodium (peripheral)	In albino mice writhing induced by acetic acid	Oral administration of nimesulide/diclofenac can be summed up by the supplementation of piperine because it inhibits the biotransformation and significantly increase the amount of drug in plasma. Co-administration can relieve the pain 1.5 times faster
Pentazocine (central analgesic)	In albino mice Tail flick method	Piperine combined with pentazocine showed a significant increase in tail flick latency in comparison with pentazocine alone, and control group follows the same mechanism as with peripheral drugs
Fexofenadine	In rats	Bioavailability can be increased up to 2-3 times than drug alone. This action of bio-potentiation is due to inhibition of P-glycoprotein efflux pump and delayed gastric emptying
SQN	Human Caco-2 cells line and male Sprague-Dawley rats	HIV-1 protease inhibitor, in the presence of piperine shows good bioavailability due to inhibition of P-glycoprotein efflux of drug from cells. This bio-enhancer improves the oral bioavailability of SQN by ~ 10 folds. Human cell line mimics the intestinal barrier

EGCG: Epigallocatechin gallate. SQN: Saquinavir mesylate

Table 2: *Anupana* according to *Dosha*

Dosha	*Anupana*
Vata	*Snigdha* and *Ushna*
Pitta	*Madhura* and *Sheeta*
Kapha	*Ruksha* and *Ushna*

Bhaishajyakala (proper time for administration of medicine)

In Ayurveda, there is description of proper time for administration of medicine in relation to food. Ten *Kala* (times) for administration of medicine in relation to food are mentioned in classics, and these may also help to increase absorption rate of drugs.[30,31] These are as follows:

- *Abhakta* - Administration of medicine after proper digestion of food, i.e., on empty stomach. Especially indicated in *Kapha Vriddhi* and for the individual with good strength
- *Pragbhakta* - If medication is given just before the meal then it is known as *Pragbhakta*. It should be prescribed to children, females, lean and thin individuals. It helps to alleviate the disorders of *Apana Vayu*
- *Adhobhakta* - Taking medication just after the meal, helps to alleviate the disorders of *Vyana Vayu*, and *Apana Vayu* and also helps to gain weight
- *Madhyabhakta* - If the medication is administered at the midway of meal, it is known as *Madhyabhakta*. It alleviates the disorders of *Samana Vayu* and the disorders affecting the middle part of the body. It should also prescribed in the disorders of *Koshtha* and *Pitta*
- *Antarabhakta* - It is the medication taken in between two meals (between morning and evening meal). It is beneficial for heart, provide mental satisfaction, improve digestion, and useful in the treatment of disorders of *Vyana Vayu*
- *Sa-bhakta* - Medication is administered by mixing with food which make drugs palatable, it termed as *Sa-bhakta*. This method is useful in the treatment of *Aruchi* and diseases of the whole body
- *Samudga* - When the medication is advised to be taken two times, before and after the meal, it is useful in *Hikka Roga*, *Kamp Roga,* and *Akshipaka*
- *Muhurmuhu* - When the drug is administered several times in a day in small divided doses. It is beneficial in *Shvasa*, *Chhardi,* etc., because there may be several exacerbating episodes of these diseases in a day
- *Sa-grasa* - Here, the drug is given by mixing with *Grasa* (bolus) of meal. *Deepana* and *Vajikarana* (aphrodisiac) drugs are administered in this way
- *Grasantara* - If the drugs are advised to be taken in between two *Grasa* of meal. This method is also used for the administration of *Deepana* and *Vajikarana* (aphrodisiac) drugs.

It is well acknowledged that Ayurveda is an ancient system of medicine which is still serving human beings in different ways. The concept of administration of drugs in relation to food

and/or time is basically originated in Ayurveda. The concept has been developed probably based on the required frequency of drug administration, their specific effects on *Doshas*, and improving the efficacy of a particular drug. This principle of drug administration has been followed in both Ayurvedic and modern medical practices, for example, *Muhurmuhu* administration of drugs in *Chhardi* and *Shvasa*, *Sa-grasa* use of *Deepana* drugs, anti-tubercular treatment, and thyroid drugs (thyroid hormone) are advised to taken at empty stomach and this leads to increased absorption and bioavailability of these drugs.

Bhavana (trituration)

It is a special method for enhancing the bioavailability of drugs. In this, the drug/drugs are triturated with the *Svarasa*, *Kvatha,* etc., of another drug during the manufacturing of dosage forms to increase the effect of the drug.[32] One important example of *Bhavana Dravya* includes *Gomutra* (cow urine). *Gomutra* is a well-established bio-enhancer of animal origin.

Cow's urine is mostly used in its distillated form and it increases the bioavailability of antimicrobial, antifungal, and anticancer agents.[33] Cow's urine distillate enhances both the release and activity of gonadotropin-releasing hormone, and ultimately increases sperm motility, sperm count, and sperm morphology in male mice.[34]

Cow urine has been granted US Patents (No. 6 896 907 and 6 410 059) for its medicinal properties, particularly as a bio-enhancer.[35] Cow urine distillate increases the activity of rifampicin by about 5–7 times against *Escherichia coli* and 3–11 times against Gram-positive bacteria. It probably acts by enhancing the transportation of antibiotics across the membrane of gastrointestinal tract. The enhancement in transport is approximately 2 to 7 times.[36] Some other important *Bhavana Dravya* includes *Ardraka Svarasa*, and *Nimbu Svarasa* (citrus).

Citrus fruits are good source of quercetin. It exhibits bio-enhancing effect by inhibiting both CYP3A4 and P-gp. Thus, it increases bio-efficacy and blood levels of large number of drugs including calcium channel blockers (verapamil, diltiazem), antineoplastics (paclitaxel, doxorubicin), digoxin, and epigallocatechin gallate.[37,38]

Classically, *Bhavana* is used to enhance/modify the potency of a particular single or compound drug. Pharmacologically, these drugs act either by bringing a small change in chemical structure of the principal drug or by increasing the bioavailability of the principal drug, and hence the same doses of the drugs bring about more effective and potent action. Thus, the process of *Bhavana* should logically be considered as an important measure for enhancing bioavailability.

Rasayana (rejuvenation by neutraceutical action)

Rasayana drugs claimed for their bio-enhancing effects include *Madhuyashti* (*Glycyrrhiza glabra* Linn.), *Draksha* (*Vitis vinifera* Linn.), *Lashuna* (*Allium sativum* Linn.), and *Ghritkumari* (*Aloe vera* Tourn. ex Linn.).

Glycyrrhizin is a triterpenoid saponin found in *G. glabra* (liquorice). Glycyrrhizin shows a more potent absorption-enhancing activity than caproic acid at the same concentration tested.[39] The absorption-enhancing activity obtained from the simultaneous treatment of sodium deoxycholate and dipotassium-glycyrrhizin was much greater than sodium deoxycholate alone in Caco-2 cell monolayers. The absorption-enhancing activity of glycyrrhizin was increased by the presence of the other absorption enhancers.[40] It also enhances cell division inhibitory activity of anticancerous drug "Taxol" by 5 folds against the growth and multiplication of breast cancer cell lines. It is reported that glycyrrhizin enhances the transport of antibiotics such as rifampicin, tetracycline, nalidixic acid, ampicillin, and Vitamins B_1 and B_{12} across the gut membrane.[41]

Draksha contains a flavonoid glycoside, naringin in its fruit juice which makes grape fruit juice taste bitter. A study was done to investigate the effect of naringin on the pharmacokinetics of quinine in rats after oral or i.v. (intravenous) dosing of quinine. Female Wistar rats (weight 190–220 g) were used in two separate studies, i.e., oral and i.v. administration of quinine. Plasma quinine concentration was assayed by HPLC. Pretreatment with naringin did not cause any significant change in the pharmacokinetics of quinine after the i.v. dose. However, pretreatment with naringin led to a 208% increase in peak plasma concentration (C_{max}), a 93% increase in time to reach C_{max} (t_{max}), and a 152% increase in the area under the plasma concentration-time curve of quinine after oral administration. Consequently, the oral bioavailability of quinine was significantly increased ($P < 0.05$) from 17% (control) to 42% after pretreatment with naringin. This bio-enhancement was achieved mainly via the inhibition of CYP3A4.[42] It is also reported that naringin increases the bioavailability of paclitaxel by inhibiting CYP3A1/2 and P-gp in rats.[43]

Lashuna (*A. sativum*) is gifted with an active bio-enhancer phytomolecule, allicin, that enhances the fungicidal activity of amphotericin B against pathogenic fungi such as *Candida albicans, Aspergillus fumigatus,* and the common yeast, *Saccharomyces cerevisiae*.[44]

A. vera is also proved as a bio-enhancer. The results of two different *A. vera* preparations, i.e., whole leaf extract and inner filled gel indicate that the aloes improve the absorption of both the Vitamin C and E. The absorption is slower and vitamins last longer in the plasma with aloes and this lead to increased bioavailability of Vitamin C and E in human. *A. vera* is a very promising future nutritional herbal bio-enhancer.[45]

Samshodhana (bio-purification)

Samshodhana is a special type of management described in Ayurvedic system of medicine. It is a type of biopurification used to eliminate the vitiated *Dosha* (morbid humors) out of the body as a preventive measure or to manage different disorders. *Samshodhana* increases the strength of *Agni*, leading to an increased digestion power and increased absorption of nutrients and drugs.[46] Thus, ultimately, it

increases the bioavailability of nutrients and drugs. The process of bio-purification also cleanses the body channels, thereby improving their patency, microcirculation, and flow of biomolecules. In Ayurveda, *Rasayana* (rejuvenative) and *Vajikarana* (aphrodisiac) drugs are advised to be taken after proper *Samshodhana* (bio-purification).[47] Proper bio-purification increases the bioavailability of *Rasayana* and *Vajikarana* drugs, thus potentiates their efficacy.

In this way, not only the *Rasayana* and *Vajikarana* drugs but also many other drugs if taken after proper *Samshodhana* therapy show increased efficacy, and this confirms the bio-enhancing effect of *Samshodhana* therapy.

There is no contrast of action between the reduction of toxicity and the bio-enhancing effect of *Samshodhana Karma*. In fact, *Samshodhana* is primarily aimed at detoxification of the body, but the entire process of *Samshodhana* ultimately leads to the better patency of the body channels (*Srotasas*). Therefore, it results into better perfusion of the drugs into the body system, thus leading to the enhanced bio-availability.

Yoga (formulations) and *Kalpanas* (various dosage forms)

Plant-based medicines of natural origin have been used by human beings since time immemorial. Ayurveda has described different types of *Kalpanas* (*Svarasa*, *Kvatha*, *Phanta,* etc.) and various formulations such as *Choorna, Avaleha, Asava, Arishta, Guggulu,* and different mineral and herbo-mineral preparations. Initially, the physicians used the drugs in coarse crude form such as *Svarasa* and *Kvatha* followed by fine crude form such as *Vati, Choorna,* and later on finer forms such as *Bhasma*. Down the ages, as the time passed, the Ayurvedic physicians realized about the low bioavailability of drugs, and this led to the concept of various other dosage forms (from crude forms to finer forms). In finer forms, drugs get more absorption and ultimately result in an increased bioavailability.

Concept of *Purana Aushadhies* (old drugs)

Some of the drugs described in Ayurveda are advised to be used after one year of collection, for example, *Vidanga, Pippali,* Jaggery, *Dhanyaka, Ghrita,* and Honey.[48] Probably, this leads to enhancement of their potency, and if they are co-administered with other drugs, they might increase the bioavailability of those drugs.

Regarding the *Purana Aushadies,* it should be clarified that this concept is not applicable to all the drugs which are kept for a long time (for 1 year or more); it is particularly applicable in reference to certain drugs/class of drugs whose examples have been given above. Keeping this class of drugs for a long time probably produces certain chemical changes in them, which makes the drug more potent. Thus, these *Purana* drugs can be said to have enhanced bioavailability when compared with the fresh drug and increases the bioavailability of co-administered drugs.

Concept of action-augmenting drugs

It is well acknowledged that some/group of supporting drugs described in the Ayurvedic system of medicine have traditionally been used successfully in association with other drugs for bio-potentiation of many principal drugs. This type of bio-enhancers included *Madhuyashti* (*G. glabra*) and *Vacha* (*Acorus calamus* Linn.), and group of drugs such as *Snehopaga, Svedopaga, Vamanopaga, Virechanopaga*, etc.[49,50] For example, *Vamanopaga* and *Virechanopaga* drugs augment the induction of *Vamana* (therapeutic emesis) and *Virechana* (therapeutic purgation) in a proper manner, respectively.

All the drugs of the *Upaga* categories promote or potentiate the action of principal drugs. As per the definition, bio-enhancers augment the bioavailability or biological activity of drugs when co-administered with principal drug at low doses. Therefore, all these drugs automatically come under the category of bio-enhancer whether they act on the concept of the synergism or by other mechanism.

Penetration enhancers

The drugs/molecules used to improve the bioavailability and range of drugs administered via topical or transdermal route are termed as skin penetration enhancers/penetration enhancers. Penetration enhancers are also called accelerants. Penetration enhancers are defined as substances that are capable of promoting penetration of drugs into skin by permeation through skin or by reversibly reducing the skin barrier resistance.

There is a considerable interest in the delivery of drugs through skin into the systemic circulation and for local effect. However, the outermost layer of the human skin, stratum corneum, presents a formidable barrier and also interferes with the absorption of topical therapeutic drugs, and drug penetration, thereby reducing bioavailability.

Skin penetration enhancement is achieved through modification of stratum corneum by hydration/chemical enhancers action on the structure of the stratum corneum lipids and keratin partitioning and solubility effects. Numerous vehicles and penetration enhancers have been synthesized to increase transdermal delivery of drugs, such as alcohols, azone, esters, glycols, fatty acids, pyrrolidones, sulfoxides, and terpenes.

In Ayurveda, use of *Lavana* (salt) along with oil for external application has been mentioned as if *Lavana* is mixed with oil, it helps to open the *Srotas* (microchannels of the body) due to its *Sukshma* and penetrating power of the oil and thus, ultimately results in the potentiation of efficacy.[51] Similarly, some other drugs are also described for the same purpose when used externally with principal drugs such as honey, *Ghrita*, and oil. Similarly, honey and/or *Ghrita* when are mixed with *Basti Dravya* (medicated enema), it might lead to an increase in the penetration of drugs used in *Basti* therapy.[52,53]

Properties of penetration enhancers

An ideal penetration enhancer should be chemically stable, non-toxic, non-irritant, and non-allergenic. It should have a rapid onset of action, predictable duration of activity, as well as a reproducible and reversible effect. It should be chemically and physically compatible with the formulation ingredients.

It should be odorless, tasteless, colorless, inexpensive, pharmaceutically and cosmetically acceptable. It should have a solubility parameter similar to that of skin.[54,55]

Future prospects

Ayurveda provides a lead to the modern researchers to find their way. Most of the allopathic molecules (almost 70%) could be traced back to nature. It has started from the first concept of *Yogavahi* using *Trikatu* as a bio-enhancer in Ayurveda which was further applied successfully to various modern medicines. The Ayurvedic concept of bio-enhancers needs to be merged with the modern medicine (synthetic medicines) for healthy effects. Some of the areas of bio-enhancement are still need to be lightened up and should highly be focused on their active principles, mechanisms of actions, clinical outcomes, toxicity evaluation, and suitable combinations with other drugs. Hence, it can be useful to explore novel principles with high bio-enhancing ability and less toxic effects.[10]

Origin of about 75% of antimicrobial and 60% of anticancer drugs approved for clinical use from 1981 to 2002 could be traced back to nature.[35,56] The Ayurvedic concept of bio-enhancing ought to be incorporated into the modern system of medicine to develop more efficacious and safe medicines with safer routes of drug administration in future also. The underlying mechanisms with their clinical outcomes can also be researched and validated further as per the latest research methodologies.[2]

Mechanisms of action of herbal bio-enhancers

There are several mechanisms of action by which herbal bio-enhancers act. Different herbal bio-enhancers may have same or different mechanisms of action. Various mechanisms of action postulated for herbal bio-enhancers are -

By increasing gastrointestinal blood supply, by modulating the active transporters located in various locations, for example, P-gp. P-gp is an efflux pump which pumps out drugs and prevents it from reaching the target site. Bio-enhancers in such case act by inhibiting the P-gp. By inhibiting gastrointestinal transit, gastric emptying time and intestinal motility. Decreasing the elimination process, thereby extending the sojourn of drug in the body by inhibiting the drug metabolizing enzymes such as CYP 3A4, CYP1A1, CYP1B2, CYP2E1, in the liver, gut, lungs, and various other locations and by inhibiting the renal clearance by preventing glomerular filtration, active tubular secretion by inhibiting P-gp and facilitating passive tubular reabsorption. Modifications in GIT epithelial cell membrane permeability. Bioenergetics and thermogenic properties. Suppression of first-pass metabolism and inhibition of drug metabolizing enzymes and stimulation of GGT activity which enhances the uptake of amino acids.[57]

Discussion

The traditional wisdom of Ayurveda may have immense utility in enhancing the bioavailability of allopathic (synthetic) drugs. If the herbal bio-enhancers are co-administered with synthetic drugs, this co-administration will provide very effective results and covers almost each and every class of drug. The factors which can enhance the bioavailability can be summarized as the concept of *Yogavahi*, *Anupana*, *Bhaishajya Kala*, *Rasayana*, various *Yoga* (formulations), *Purana Aushadhies*, action-augmenting drugs, penetration enhancers, and the process of *Samshodhana* and *Bhavana*.

Bioavailability is the best way to reduce dose, toxicity, and cost of drug. Therefore, use of herbal bio-enhancers with the core drug is the best way to achieve this target. Uses of such agents are applicable not only for humans but also for animals in normal practices, whether it is a medicine or for nutritional purpose.[58]

In developing countries such as India, cost of treatment is the major concern for modern medicines and scientific society has its eyes on the reduction of cost of mediciine and indirectly the whole treatment. Bio-enhancers may decrease the usual dose of drugs and neutraceuticals and thus ultimately reduce the drug-resistance, toxicity, and shorten the period of treatment.

Since the oral route is the most common and easy route of drug administration, significant drug absorption and appropriate drug delivery are pre requisites for successful oral treatment of diseases. It is also well recognized that the design and composition of the pharmaceutical dosage form may have an important impact on the bioavailability and hence therapeutic outcome of a drug product. This includes both intentional effects such as altered drug absorption rates by modified release or different forms of formulations or increased bioavailability for dosage forms including absorption-enhancing principles, as well as undesirable effects such as reductions in the amount of drug reaching the systemic circulation (to modify the bioavailability) due to poor product design. Ayurvedic bio-enhancing drugs such as *Pippali*, their processes such as *Bhavana*, different dosage forms such as *Kalpanas* and various formulations and the procedures such as *Samshodhana* would probably work by the above mechanisms and are intended to bring about these favorable changes into the drugs.

Allopathic modernization is all about novel chemical entities with a new mode of action that affects the cost of development. Reverse pharmacology is a revolutionary breakthrough to identify active therapeutic agents at minimal cost of drug discovery. Cost-effective and cheap allopathic cure can be provided to each and every section of society whether they are not financially sound by the integrated approach. Animal-originated cow urine distillate is also a milestone in this category of medicinal field. Therefore, this integration of tradition and technology can satisfy all necessary criteria of safe and ideal combination.

Different bio-enhancing drugs, their processing, formulations, and procedures enhance bio-availability by same or different mechanisms which include inhibition of metabolizing enzymes responsible for drug metabolism and degradation,

increase in gastrointestinal blood supply, and inhibition of glucuronic acid conjugation, by modifying GIT epithelial cell membrane permeability, stimulation of gamma glutamyl transpeptidase, etc. The benefits of bio-enhancing include increased bioavailability and efficacy, reduced adverse drug reaction or side effects, improvement in oral absorption of a wide range of nutrients such as vitamins, minerals, and amino acids, reduced resistance of drug, decreased requirement of raw material for drug manufacturing, and thus benefited to world economy by reducing the cost of dosage form and ultimately the whole treatment.

Conclusion

The present review acknowledges the different aspects of herbal bioavailability enhancers including historical aspects, different concepts, and methods used in Ayurveda with their probable evidence-based mechanism of action and techniques based on chemical and pharmaceutical means for herbal medicine. In developing countries such as India, cost of treatment is the major concern for modern medicines. Scientific society has its eyes on the reduction of dosage and indirectly cost of the whole treatment. Bio-enhancers have decreased the usual dose, hence ultimately reduces the drug-resistance, toxicity, and shortens the period of treatment. The traditional wisdom of Ayurveda could have immense utility in enhancing the bioavailability of allopathic drugs. If the traditional wisdom of Ayurveda is coupled with the modern technologies, it would open new vistas in the public health care.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Breedveld P, Beijnen JH, Schellens JH. Use of P-glycoprotein and BCRP inhibitors to improve oral bioavailability and CNS penetration of anticancer drugs. Trends Pharmacol Sci 2006;27:17-24.
2. Muttepawar SS, Jadhav SB, Kankudate AD, Sanghai SD, Usturge DR. A review on bioavailability enhancers of herbal origin. World J Pharm Pharm Sci 2014;3:667-77.
3. Kesarwani K, Gupta R, Mukerjee A. Bioavailability enhancers of herbal origin: An overview. Asian Pac J Trop Biomed 2013;3:253-66.
4. Singh J, Dubey RK, Atal CK. Piperine-mediated inhibition of glucuronidation activity in isolated epithelial cells of the guinea-pig small intestine: Evidence that piperine lowers the endogeneous UDP-glucuronic acid content. J Pharmacol Exp Ther 2002;302:645-50.
5. Johri RK, Zutshi U. An Ayurvedic formulation "Trikatu" and its constituents. J Ethnopharmacol 1992;37:85-91.
6. Atal CK, Zutshi U, Rao PG. Scientific evidence on the role of Ayurvedic herbals on bioavailability of drugs. J Ethnopharmacol 1981;4:229-32.
7. Bano G, Amla V, Raina RK, Zutshi U, Chopra CL. The effect of piperine on pharmacokinetics of phenytoin in healthy volunteers. Planta Med 1987;53:568-9.
8. Bano G, Raina RK, Zutshi U, Bedi KL, Johri RK, Sharma SC. Effect of piperine on bioavailability and pharmacokinetics of propranolol and theophylline in healthy volunteers. Eur J Clin Pharmacol 1991;41:615-7.
9. Shashtri KA, editor. Sushruta Samhita of Sushruta, Sutra Sthana, Ch. 45, Ver. 142. 14th ed. Varanasi: Chaukhambha Sanskrit Sansthan; 2003. p. 181.
10. Bharat J, Somdatt G. Bio-potentiation using herbs: Novel Technique for poor bioavailable drugs. Int J PharmTech Res 2014;6:443-54.
11. Bhardwaj RK, Glaeser H, Becquemont L, Klotz U, Gupta SK, Fromm MF. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. J Pharmacol Exp Ther 2002;302:645-50.
12. Reen RK, Jamwal DS, Taneja SC. Impairment of UDP-glucose dehydrogenase and glucuronidation activities in liver and small intestine of rat and guinea pig *in vitro* by piperine. Biochem Pharmacol 1993;46:229-38.
13. 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 Ther 1985;232:258-62.
14. Stöhr JR, Xiao PG, Bauer R. Constituents of Chinese Piper species and their inhibitory activity on prostaglandin and leukotriene biosynthesis *in vitro*. J Ethnopharmacol. 2001;75:133-9.
15. Dudhatra GB, Mody SK, Awale MM, Patel HB, Modi CM, Kumar A, *et al.* A comprehensive review on pharmacotherapeutics of herbal bioenhancers. ScientificWorldJournal 2012;2012:637953.
16. 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 acid and lipid peroxidation. Biochem Pharmacol 1992;43:1401-7.
17. Balakrishnan V, Varma S, Chatterji D. Piperine augments transcription inhibitory activity of rifampicin by several fold in *Mycobacterium smegmatis*. Curr Sci 2001;80:1302-5.
18. Bharat J, Somdatt G. Biopotentiation using herbs: Novel technique for poor bioavailable drugs. Int J PharmTech Res 2014;6:443-54.
19. Mujumdar AM, Dhuley JN, Deshmukh VK, Raman PH, Thorat SL, Naik SR. Effect of piperine on pentobarbitone induced hypnosis in rats. Indian J Exp Biol 1990;28:486-7.
20. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med 1998;64:353-6.
21. Lambert JD, Hong J, Kim DH, Mishin VM, Yang CS. Piperine enhances the bioavailability of the tea polyphenol (-)-epigallocatechin-3-gallate in mice. J Nutr 2004;134:1948-52.
22. Badmaev V, Majeed M, Prakash L. Piperine derived from black pepper increases the plasma levels of coenzyme Q10 following oral supplementation. J Nutr Biochem 2000;11:109-13.
23. Gupta SK, Velpandian T, Sengupta S, Mathur P, Sapra P. Influence of piperine on nimesulide induced antinociception. Phytother Res 1998;12:266-9.
24. Pooja S, Agrawal R, Nyati P, Savita V, Phadnis P. Analgesic activity of *Piper nigrum* and its interaction with diclofenac sodium and pentazocine in albino mice. Int J Pharmacol 2007;5:30.
25. Jin MJ, Han HK. Effect of piperine, a major component of black pepper, on the intestinal absorption of fexofenadine and its implication on food-drug interaction. J Food Sci 2010;75:H93-6.
26. Sudipta B, Himanshu R, Patel Vandana B, Hitesh P. Effect of herbal bio-enhancers on Saquinavir in human caco- 2 cell monolayers and pharmacokinetics in rats. International J Med Pharm Sci 2012;2:27-41.
27. Shashtri RD, editors. Charaka Samhita of Agnivesha, Sutra Sthana, Ch. 27, Ver. 326. Reprint ed. Varanasi: Chaukambha bhaarti Academy; 2005. p. 564.
28. Shashtri RD, editors. Charaka Samhita of Agnivesha, Sutra Sthan, Ch. 27, Ver. 321. Reprint ed. Varanasi: Chaukambha bhaarti Academy; 2005. p. 563.
29. Shashtri KA, editor. Sushruta Samhita of Sushruta, Sutra Sthana, Ch. 46, Ver. 435. 14th ed. Varanasi: Chaukhambha Sanskrit Sansthan; 2003. p. 226.
30. Shashtri KA, editor. Sushruta Samhita of Sushruta, Uttara Tantra, Ch. 64, Ver. 67. 14th ed. Varanasi: Chaukhambha Sanskrit Sansthan; 2003. p. 489.
31. Tripathi R, editor. Ashtanga Sangraha of Vagabhata, Sutra Sthana, Ch. 23, Ver. 12. Reprint ed. Delhi: Chaukhambha Sanskrita Pratisthan; 2001. p. 428.
32. Shashtri RD, editor. Charaka Samhita of Agnivesha, Kalpa Sthana, Ch. 12, Ver. 47. Reprint ed, Varanasi: Chaukambha bhaarti Academy; 2005. p. 945.
33. Kekuda PT, Nishanth BC, Kumar Praveen SV, Kamal D, Sandeep M,

Megharaj HK. Cow urine concentrate: A potent agent with antimicrobial and anthelmintic activity. J Pharm Res 2010;3:1025-7.
34. Ganaie JA, Shrivastava VK. Effects of gonadotropin releasing hormone conjugate immunization and bioenhancing role of Kamdhenu ark on estrous cycle, serum estradiol and progesterone levels in female *Mus musculus*. Iran J Reprod Med 2010;8:70-5.
35. Randhawa GK, Kullar JS, Rajkumar. Bioenhancers from mother nature and their applicability in modern medicine. Int J Appl Basic Med Res 2011;1:5-10.
36. Chawla PC. Resorine – A novel CSIR drug curtails TB treatment. CSIR News 2010;60:52-4.
37. Choi JS, Li X. Enhanced diltiazem bioavailability after oral administration of diltiazem with quercetin to rabbits. Int J Pharm 2005;297:1-8.
38. Wang P, Heber D, Henning SM. Quercetin increased bioavailability and decreased methylation of green tea polyphenols *in vitro* and *in vivo*. Food Funct 2012;3:635-42.
39. Imai T, Sakai M, Ohtake H, Azuma H, Otagiri M. Absorption-enhancing effect of glycyrrhizin induced in the presence of capric acid. Int J Pharm 2005;294:11-21.
40. Sakai M, Imai T, Ohtake H, Azuma H, Otagiri M. Simultaneous use of sodium deoxycholate and dipotassium glycyrrhizinate enhances the cellular transport of poorly absorbed compounds across Caco-2 cell monolayers. J Pharm Pharmacol 1999;51:27-33.
41. Sushma D, Smriti K, Sheveta B, Pratush L. Use of herbal bio-enhancers to increase the bioavailability of drugs. Res J Pharm Biol Chem Sci 2011;2:107.
42. Zhang H, Wong CW, Coville PF, Wanwimolruk S. Effect of the grapefruit flavonoid naringin on pharmacokinetics of quinine in rats. Drug Metabol Drug Interact 2000;17:351-63.
43. Lim SC, Choi JS. Effects of naringin on the pharmacokinetics of intravenous paclitaxel in rats. Biopharm Drug Dispos 2006;27:443-7.
44. 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;72:1247-50.
45. Vinson JA, Al Kharrat H, Andreoli L. Effect of *Aloe vera* preparations on the human bioavailability of Vitamins C and E. Phytomedicine 2005;12:760-5.
46. Shashtri RD, editor. Charaka Samhita of Agnivesha, Sutra Sthana, Ch. 16, Ver. 17. Reprint ed. Varanasi: Chaukambha Bharti Academy; 2005. p. 321.
47. Shashtri RD, editor. Charaka Samhita of Agnivesha, Chikitsa Sthana, Ch. 1/1, Ver. 24. Reprint ed. Varanasi: Chaukambha bhaarti Academy; 2005. p. 9.
48. Murthy PM, editor. Sharangadhar Samhita of Sharangadhara, Poorva Khanda, Ch. 1, Veer. 44. 1st ed. Varanasi: Chaukhambha Sanskrit Series Office; 2001. p. 8.
49. Shashtri RD, editor. Charaka Samhita of Agnivesha, Sutra Sthana, Ch. 2, Ver. 7-9. Reprint ed. Varanasi: Chaukambha Bhaarti Academy; 2005. p. 52, 53.
50. Shashtri RD, editor. Charaka Samhita of Agnivesha, Sutra Sthana, Ch. 4, Ver. 8. Reprint ed. Varanasi: Chaukambha bhaarti Academy; 2005. p. 70.
51. Shashtri RD, editor. Charaka Samhita of Agnivesha, Sutra Sthana, Ch. 13, Ver. 98. Reprint ed. Varanasi: Chaukambha Bhaarti Academy; 2005. p. 280.
52. Tripathi B, editor. Ashtanga Hridaya of Vagabhatta, Sutra Sthana, Ch. 19, Ver. 38-40. Reprint ed. Delhi: Chaukhambha Sanskrita Pratisthana; 2003. p. 235.
53. Shashtri RD, editor. Charaka Samhita of Agnivesha, Chikitsa Sthana, Ch. 2/4, Ver. 10. Reprint ed. Varanasi: Chaukambha Bhaarti Academy; 2005. p. 85.
54. Pfister WR, Hsieh DS. Permeation enhancers compatible with transdermal drug delivery systems. Part I: Selection and formulation considerations. Med Device Technol 1990;1:48-55.
55. Muttepawar SS, Jadhav SB, Kankudate AD, Sanghai SD, Usturge DR, Chavare SS. A review on bioavailability enhancers of herbal origin. World J Pharm Pharm Sci 2014;3:667-77.
56. Patwardhan B, Vaidya AD. Natural products drug discovery: Accelerating the clinical candidate development using reverse pharmacology approaches. Indian J Exp Biol 2010;48:220-7.
57. Singh S, Tripathi JS, Rai NP. An integrated approach to the bioavailability enhancers. In: Rao RK, *et al*., editor. Recent Advances on the Role of Basic Sciences in Ayurvedic Medicine. 1st ed. Varanasi: Mahima Publications; 2014. p. 424-34.
58. Ratndeep S, Devi Sarita B, Patel Jatin H, Patel Urvesh D. Indian herbal bio-enhancers: A review. Phcogn Rev2009;3:80-2.

हिन्दी सारांश

आयुर्वेद में जैव उपलब्धता परिवर्धित क्रिया का मूल्यांकन - फॉर्माकोलॉजीकल तकनीकों के आधार पर

सत्यपाल सिंह, जे एस त्रिपाठी, एन पी राय

आधुनिक चिकित्सा पद्धति में जैव उपलब्धता परिवर्धित क्रिया, एक नया विचार है परंतु यह संकल्पना आयुर्वेद में पहले से ही प्रयोग की जाती रही है। जैव वृद्धि करने वाले तत्व औषधों की जैव उपलब्धता को बढ़ाने के कारण कम मात्रा में प्रमुख औषधि के साथ प्रयोग किया जाता है। आयुर्वेद में जैव वृद्धि हेतु कुछ औषधियों जैसे कि पाइपर लोंगम लिन., जिंजिबर ओफिसिनेल रोज और ग्लाइसेराइजा ग्लेब्रा लिन. तथा ऐसी विभिन्न पद्धतियों का उपयोग किया जा रहा है। जैव वृद्धि का हेतु प्रमुख औषध की चिकित्सीय मात्रा में कमी से औषधियों की विषाक्तता और उसके विपरीत प्रभाव को कम करना, प्रतिरोध को कम करना अंततः इससे दवा निर्माण के लिए कच्चे माल की आवश्यकता घट जाती है और इस प्रकार होने पर विश्व आर्थिक व्यवस्था को लाभ होता है। इस समीक्षा में आयुर्वेदिक चिकित्सा पद्धति में वर्णित प्राकृतिक जैव वृद्धि कारकों को तथा इसके विभिन्न तकनीकों का संग्रह कर, इन पद्धतियों पर विचार किया गया है। इस तरह जैव वृद्धि को बढ़ाने वाले विभिन्न तरीकों को जिसमें चिकित्सीय तकनीक जैसे शोधन, औषध जैसे कि पिप्पली और कार्यकारी शक्ति उदाहरण के लिए योगवाही और रसायन, इन सबका विवरण आयुर्वेद में उपलब्ध संदर्भों के आधार पर किया गया है।