Ayurvedic bioenhancers: A classical and contemporary review

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Definition of bio-enhancer

- A **bioenhancer** is an agent capable of enhancing the bioavailability and efficacy of a drug with which it is co-administered, without any pharmacological activity of its own at therapeutic dose used.
Herbal bioenhancer

Herbal bioenhancer is an agent of herbal origin or any phytomolecule, which is capable of enhancing bioavailability and bioefficacy of a particular drug or nutrient with which it is combined, without any typical pharmacological activity of its own at the dose used.
In the 1920’s, Bose, an acknowledged author of “Pharmacographia Indica,” reported an enhanced antiasthmatic effect of an Ayurvedic formula containing *vasaka* (*Adhatoda vasica*) when administered with *long pepper*.
• The term bioavailability enhancer was first coined by Indian Scientists at the Regional Research laboratory, Jammu (RRL, now known as Indian Institute of Integrative Medicine) discovered and scientifically validated *piperine* as the world’s first bioavailability enhancer in 1979
• The term bioavailability or bioenhancing activity is defined as “a substance at a lower dosage level, which in combination with a drug or nutrient provides more availability of the drug by reducing the consumption of the drug or nutrient resulting in enhanced efficacy of the drugs.”
Why the interest in modern medicine?

• The great interests for the improvement of bioavailability of a large number of drugs are-
  • (1) poorly available,
  • (2) administered for long periods,
  • (3) toxic, and
  • (4) expensive.
• Maximizing bioavailability is therapeutically important because the extent of bioavailability directly influences plasma concentrations and consequently therapeutic efficacy.

• Bioavailability enhancement can make the expensive drugs affordable and reduce the toxic effects by reducing the required dose of drugs.
The benefits of adding a bioenhancer

• reduced drug dosage
• reduced cost of the drug
• reduced incidence of drug resistance
• and reduced risk of adverse drug reaction/side effects.
• Moreover, efficacy is enhanced by increased bioavailability.
• Secondary beneficial effects include reduced requirement of raw material for drug manufacture.
Mechanism

- (a) Promoting the absorption of the drugs from GIT.
- (b) Inhibiting or reducing the rate of biotransformation of drugs in the liver or intestines.
- (c) Modifying the immune system in such a way that the overall requirement of the drug is reduced substantially.
Mechanism

• (d) Increasing the penetration or the entry into the pathogens even where they become persistors within the macrophages such as for *Mycobacterium tuberculosis* and such others.

• This eventually ensures the enhanced killing of these organisms is well secured within the places otherwise inaccessible to the active drug.
• (e) Inhibiting the capability of pathogens or abnormal tissue to reject the drug, for example, efflux mechanisms frequently encountered with antimalarial, anticancer and antimicrobial drugs.
• (f) Modifying the signaling process between host and pathogen ensuring increased accessibility of the drugs to the pathogens.

• (g) Enhancing the binding of the drug with the target sites such as receptors, proteins, DNA, RNA, and the like in the pathogen, thus potentiating and prolonging its effect leading to enhanced antibiotic activity against pathogens.
• (h) Besides these, the bioenhancer agents may also be useful for promoting the transport of nutrients and the drugs across the blood brain barrier, which could be of immense help in the control of diseases like cerebral infections, epilepsy, and other CNS problems
In Ayurveda

- Yogavahi
- Deepana pacana
- Processes to increase bioavailability:-
  - Sneha paka
  - Ksheerapaka
  - Bhavana
  - Marana
  - Anupana
YOGAVAAHEE Dravya

- Madhu
- Ghrta
- Guggulu
- Shilajatu
- Parada
- Kajjali
- Rasa sindura
- Bhasma
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Madhu-Yogavahi

- Honey is called as “Yogavahi” The substance which has a quality of penetrating the deepest tissue is called as Yogavahi.

- When honey is used with other herbal preparations it enhances the medicinal qualities of those preparations and also helps them to reach the deeper tissues.
Bhasma as Yogavahi

• All Bhasmas have common properties like Rasayana, Yogavahi etc.
• Rasayana indicates immunomodulation and anti-aging properties
• Yogavahi indicates ability of drug carry and targeted drug delivery by Bhasmas
• These are prescribed in very minute dose (alpamaatraa)
• Under *Rasibhavana*, properly prepared Bhasma must be readily absorbable, adaptable and assimilable in the body and will be non toxic.

• *Shighrayavyapti* indicates that after *Marana*, *Bhasma* becomes easily absorbable and assimilable and spreads quickly in the body.

• Under *Agnideepana*, *Bhasma* increases metabolism at cellular level and acts as catalyst.
Bhasma as Yogavahi

• These attributes of Bhasma are comparable with the action of Nanoparticles in the body
• These are biodegradable, biocompatible and non-antigenic in nature.
• Nanoparticles in general can be used to provide selected/targeted/controlled delivery of drugs to specific site of action even across the blood-brain barrier.
Attributes of Bhasma

• These can be used to extend time window of bioavailability and to protect drug from chemical and enzymatic decomposition.

• These can also result in reduction of peripheral side effects of drugs by decreasing overall dose of drugs in the body
• Comparable with liposomal drug delivery system
• Solid lipid nanoparticles are formed
• Better bioavailability, better transdermal absorption
• Drugs encapsulated in liposomes are expected to be transported without rapid degradation and minimum side effects to the recipients.

  • -Neetu Singh, Anand Chaudhary
In any preparation of milk, on gradual increase in temperature the solubility of fat and protein in the media also increases which may enhances the extraction of the medicinally important active constituents and retains in the media.

It would also be supportive in the absorption of the medicament.

As milk is a colloidal solution it is the most efficient media for extraction of medicaments and can be easily absorbed through the body membranes.

**KSHEERA PAKA TO ENHANCE BIOAVAILABILITY**
Bhavana - a process to enhance bioavailability

• By the process of Bhavana, with the liquids like herbal juice, the potency of the drug is enhanced.

• eg; Amalaki Rasayana

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**Bhavana** - a process to enhance bioavailability

- **Mechanism:**
  - Reduction in particle size
  - Formation of nanoemulsion
  - Formation of biological complexes
Marana—a process to enhance bioavailability

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Changes during *Marana* process:

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- AlÉmxÉÑqÉeeÉlÉÇ UåZÉÉmÉÔhÉïiÉÉ mÉÑOûiÉÉå

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Anupana

- In the context of food, Anupana helps in its better digestion and absorption and provides complete nourishment to the body.
- It helps not only for palatability but mainly for carrying the drug to target site by which it increase its absorption in target place.

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Anupana

• In modern system of medicine the term Anupana may be taken for vehicle, adjuvant or carrier through which the action like drug absorption, drug companion and the drug interaction are performed.

• Honey is the best Anupana for drugs due to its Yogavahi Guna

• Goghrta is also a good bio-enhancer
EXAMPLES OF BIOENHANCERS IN AYURVEDA
TRIKATU

• *Trikatu* are used in a number of formulations as ingredients eventhough many a times they may not have a direct role to play in the disease indicated for the formulation.

• TRIKATU is a combination of black pepper (*Piper nigrum* Linn.), long pepper (*Piper longum* Linn.), and ginger (*Zingiber officinale* Rosc.), which contains active component piperine, which enhances the bioavailability of drugs, nutrients, and vitamins.
TRIKATU

Pippali (*Piper longum*)  Maricha (*Piper nigrum*)  Shunthi (*Zingiber officinale*)
C.K. Atal, the Director of the RRL Jammu 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.
He posed two questions, ‘Why is Trikatu used in so many different formulations?’ and ‘Is it effective against all those diseases’?

He formed the working hypothesis that Trikatu increased the efficacy of formulations. Trikatu has three ingredients: black pepper (*Piper nigrum*), long pepper (*Piper longum*) and ginger (*Zingiber officinale*).

Based on this hypothesis, these ingredients were studied by a research team led by Usha Zutshi, which found that one of the ingredients, ‘Piper longum’, ‘Piper’ increased the bioavailability of many drugs.

Piperine, the active principal present in Piper longum was isolated and its bioavailability enhancing action was established.
Further research on several classes of drugs including antitubercular, leprosy, antibiotics, NSAIDS, CVS and CNS drugs showed similar results.

Piperine was found to increase bioavailability of different drugs ranging from 30 to 200%. Subsequent research has shown that it increases curcumin bioavailability by almost ten-fold.
MECHANISM OF ACTION OF PIPERINE AS A BIOENHANCER

Different mechanisms for the bioenhancer activity of piperine have been proposed including:

- DNA receptor binding
- modulation of cell signal transduction
- and inhibition of drug efflux pump.
- In general, it inhibits drug metabolizing enzymes,
- stimulates absorption by stimulating gut amino acid transporters,
- inhibits the cell pump responsible for drug elimination from cells
- and inhibits intestinal production of glucuronic acid, thus permitting a more active form of drug to enter the body.
Mechanism...

• It may increase the absorption of drug in the GIT,
• or inhibit enzymes responsible for drug metabolism, especially in the liver when the drug passes through the liver after absorption from GIT.
• Oral administration of piperine in rats strongly inhibited the hepatic arylhydrocarbon hydroxylase (AHH) and UDP-glucuronyltransferase activities
• Some of the metabolizing enzymes inhibited or induced by piperine include CYP1A1, CYP1B1, CYP1B2, CYP2E1, CYP3A4 etc.

• Most of the drugs metabolized by these enzymes will therefore be influenced by bioenhancers.
• Some other suggested mechanisms include-
  making target receptors more responsive to drugs,
• acting as receptors for drug molecules,
• increasing GIT vasculature by vasodilation to increase absorption of drugs,
• modulation of the cell membrane dynamics to increase transport of drugs across cell membranes
Shunthi as a bioenhancer

- The major pungent compounds in *Zingiber officinale* (Ginger) of rhizome extract contain potentially active gingerols, which can be converted to shogaols, zingerone, and paradol.

- Ginger acts powerfully on GIT mucous membrane.

- The role of ginger is to regulate intestinal function to facilitate absorption.

- The composition containing *Z. officinale* alone provides bioavailability/bioenhancing activity in the range of 30–75%, and piperine and *Z. officinale*, and provides the bioavailability of drugs in the range of 10–85%.
Shunthi-Zingiber officinale
**Shigru as a bioenhancer**

- Niaziridin is a nitrile glycoside that has been isolated from the leaves, pods, and bark of Drumstick (Moringa oleifera)

- It enhances bioactivity of commonly used antibiotics such as rifampicin, ampicillin, tetracycline, and nalidixic acid against Gram-positive bacteria like *M. smegmatis and Bacillus subtilis* and Gram-negative bacteria like *E. coli*
Shigru - Moringa oleifera
Yashtimadhu as bioenhancer

- Glycyrrhizin is a glycoside obtained from roots and stolon of Liquorice (Glycyrrhiza glabra).
- The anticancerous activity of Taxol in terms of inhibiting the growth and multiplication of MCF-7 cancer cells was markedly enhanced by 5-fold by adding glycyrrhizin.
- The cancerous cells growth inhibition by Taxol (0.01 μg/mL) in presence of glycyrrhizin (1 μg/mL) was higher than even the treatment with Taxol (0.05 μg/mL) alone.
Yashtimadhu (Glycyrrhiza glabra)
Glycyrrhizin as a bioenhancer

- Glycyrrhizin also enhances the bioactivity of commonly used antibiotics such as rifampicin, ampicillin, tetracycline, and nalidixic acids
- It enhances the activity ofazole antifungal drugs such as clotrimazole against *Candida albicans*
Shveta Jeeraka a bioenhancer

• The composition contain *Cuminum cyminum* extract or the fractions there of which provides bioavailability/bioenhancing activity in the range of 25–335%

• Polar and nonpolar extract of parts of *Cuminum cyminum* and *piperine* increased bioavailability in the range of 25–435%
Shveta Jeeraka - Cuminum cyminum
Krshna Jeeraka as a bio-enhancer

- *Carum carvi* (*Caraway*) contains *caraway* oil obtained from dried and crushed seeds.
- Carvone and limonene are the chief constituents of the oil.
- It has been reported to enhance bioavailability of antibiotics, antifungal, antiviral, and anticancerous drug.
Carum carvi (Caraway)
Lashuna a bioenhancer

• Allicin is an allyl sulfur containing compound obtained from Garlic (*Allium sativum*).

• *Allicin* enhances the fungicidal activity of amphotericin B.

• Cu\(^{2+}\) showed a dose-dependent fungicidal activity against *Saccharomyces cerevisiae* cells, and its lethal effect was extremely enhanced in the presence of allicin.
Lashuna - Allium sativum
Kumari as a bio-enhancer

- *Aloe vera had a* salutary effect on both vitamin C and vitamin E.
- *Aloe vera* gel and whole leaf extracts shown increased plasma concentration and improved absorption of both, vitamin C and vitamin E.
- *Aloe vera is unique in its* ability to increase bioavailability of both of these vitamins and should be considered as a *future nutritional herbal bioenhancer*
Haridra improves bioavailability

- Curcumin is the principal curcuminoid of the popular Indian spice turmeric (*Curcuma longa*).
- Curcumin suppresses drug metabolizing enzymes (CYP3A4) in the liver as well as inducing changes in the drug transporter P-glycoprotein, hence increasing the $C_{max}$ and AUC of celiprolol and midazolam in rats.
Haridra-Curcuma longa
Gomutra exhibits the property of Rasayana tattwa responsible for modulating various bodily functions, including immunity.

It augments B- and T-lymphocyte blastogenesis; and IgG, IgA and IgM antibody titers in mice.

It also increases secretion of interleukin-1 and interleukin-2, phagocytic activity of macrophages, and is thus helpful in the prevention and control of infections.
Cow Urine (Gomutra) has therapeutic values mentioned in Ayurveda and its pharmaceutical composition containing antibiotic.

Cow urine distillate as a bioenhancer was granted a US patent.

Observation concluded that cow urine and cow urine distillate increased the activity of antibiotics against tested bacterial pathogens.

Cow urine distillate was more effective bioenhancer than cow urine in combination with antibiotics.
Cow urine has bioenhancing activity for Rifampicin, the front-line anti-tubercular drug used against tuberculosis, increasing its action up to sevenfold against *Escherichia coli*, and up to 11-fold against Gram-positive bacteria.

Cow urine distillate enhances the transport of antibiotics, e.g., Rifampicin, Tetracycline, and Ampicillin, across the gut wall as well as across artificial membranes.

Transport enhancement varies from approximately twofold to sevenfold.
Cow urine has been observed to increase the potency of “Taxol” (paclitaxel) against MCF-7, a human breast cancer cell line, in in vitro assays (US Patent No. 6,410,059).

Gomutra a bioenhancer
IN RASASHASTRA
Kajjali-a bioavailability enhancer
• Kajjali, is reported in ancient Ayurvedic literature to have *yogavahi* property, i.e. it enhances the activity of drugs co-administered with it.

• This study examined the effect of Kajjali on the single dose oral pharmacokinetics of Rifampicin in healthy Wistar rats.

• Two groups (n=6) were employed one receiving single dose of Rifampicin alone and other received Kajjali (15 mg/kg, p.o.) with Rifampicin (10 mg/kg, p.o.).
• Blood samples were collected up to 10 h to estimate the plasma levels of Rifampicin.
• Further effect of Kajjali on testosterone metabolism was investigated in vitro in rat liver microsomes.
• The formation of 6α-hydroxy testosterone from testosterone was used as an index of CYP3A activity in rat liver microsomes under control conditions and in the presence of varying concentrations of Kajjali.

• Kajjali was found to be a weak inhibitor of CYP3A with a 50% decrease in enzyme activity occurring at a concentration of ~50 µg/ml (IC50) in rat liver microsomes.

• In rats, co-administration with Kajjali increased the Cmax, AUC and t1/2 of Rifampicin by ~1.75, 1.5 and 1.35-fold, respectively.
• Thus, bioavailability enhancement is the possible mechanism of increased activity of drugs co-administered with Kajjali, which could be due to inhibition of first-pass intestinal metabolism as in the case with Rifampicin.

Bioavailability of Mercury in Shwaskuthar Rasa with variations in concentrations specially of Marich[\textit{Piper nigrum}] a bioavailability enhancer

-Trupti Patil Bhole, Asmita Wele

• Two standard samples of Shwasakuthar Rasa varying in proportion of shuddha Parada 7.14% and 11.1% and that of marich 60% and 22.2% in S1 and S2 respectively were studied.

• After administration of 250mg dosage of the S1 and S2 to 8 patients, blood samples were collected at 0, 1, 1.5 and 2 hours and tested by AAS coupled with hydride generation technique for mercury content.
• **Results:**

• It is evident that mercury gets absorbed from both the formulations in trace levels.

• There is no significant difference in absorbance at 1.5 hrs\(P=0.038607\) but there is highly significant difference in absorbance at 2 hours\(P=0.002248\).

• Hg level from S1 is significantly higher than S2.

• If the variation in the amount of mercury in both formulations is taken into consideration, the increase of absorbance of mercury from S1 can be attributed to three times higher levels of *Maricha* in it.

• The Mean Residual Time (MRT) of blood Hg level is also higher in case of S2\(\text{MRT}=81.5\) minutes\] than S2 sample\(\text{MRT}=70.03\) min.].
• **Interpretation:**

• Maricha is responsible for higher bioavailability of Hg from S1 sample.

• Process of triturating one by one Maricha may also be responsible for higher level of Hg absorbance, from a comparatively less amount in the S1 formulation.
CONCLUSION

• Concept of bioavailability enhancer is rather new to western medicine but an integral part of drug design and development in Ayurveda

• Yogavahi, Deepana Paacana Dravya and Rasayana Dravya are useful to improve bioavailability

• Rasoushadhi have unique role as bioenhancers

• Various processes like Bhavana, Marana, use of suitable Anupana and Sahapana are to be planned to enhance the bio-availability of the drugs
REFERENCES

• Caraka Samhita
• Sushruta Samhita
• Ashtanga Sangraha
• Ashtanga Hridaya
• Sharngadhara Samhita
• Bhava Prakasha
• Gurpreet Kaur Randhawa et al, Bioenhancers from mother nature and their applicability in modern medicine: available at www.ijabmr.org
• Navin Atal, K.L Bedi, Bioenhancers-revolutionary concept to market available at www.jaim.in
THANK YOU