Tuijin Jishu/Journal of Propulsion Technology
ISSN: 1001-4055
Vol. 44 No. 06 (2023)

A Comprehensive Overview of Herbal Bioenhancers

Mr. Rakesh Dhole [1*], Dr. Avani Khristi[2]

1. Ph.D Scholar Department of Quality Assurance, Parul Institute of Pharmacy, Limda Waghodia Road, Vaghodia, Vadodara District, Gujarat, 391760.
2. Professor Parul Institute of Pharmacy, Limda Waghodia Road, Vaghodia, VadodaraDistrict, Gujarat, 391760.

Corresponding Author:

Mr. Rakesh Dhole

PhD Scholar Department of Quality Assurance, Parul Institute of Pharmacy, Limda Waghodia Road, Vaghodia, Vadodara District, Gujarat, 391760.

***Abstract*:**

The global use of herbal medicines has seen a notable increase due to their therapeutic benefits and fewer adverse effects compared to modern pharmaceuticals. However, the efficacy of manyherbal drugs and extracts is hindered by poor lipid solubility and improper molecular size, resulting in suboptimal absorption and limited bioavailability. Recent advancements in technology have introduced novel drug delivery systems, including liposomes, microspheres, nanoparticles, transferosomes, ethosomes, and lipid-based systems, aiming to enhance the bioavailability of herbal medications. Compounds such as quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin, and nitrile glycoside have shown promise in improving bioavailability. This review provides a comprehensive overview of these novel drug delivery technologies, shedding light on their potential to achieve better therapeutic responses. The focus extends to a compilation of bioavailability enhancers of herbal origin, delving into their mechanisms of action and highlighting studies demonstrating enhanced drug bioavailability. Noteworthy additions to this exploration include the contributions of Bacopa Monnieri and Moringa oleifera, further enriching the understanding of herbal bioavailability enhancement.

***Keywords**: Herbal medicines, bioavailability, drug delivery systems, lipid solubility.*

Introduction

The use of herbal medicine is ancient and has been practiced for as long as humanity has existed. In the last century, scientists have studied many plant extracts to understand their chemical makeup and confirm what traditional medicine has been telling us for generations[1]. Ayurveda, a traditional system of medicine, has played a big role in discovering new drugs through reverse pharmacology. This has helped identify active compounds and reduce the costsof developing drugs [2].

Now, there's a new way of using Ayurveda to make medicines work better. This technology focuses on improving the bioavailability of drugs, changing the way we administer medicines. While we've long known that various plant products can boost overall health, there's a growing interest and medical need to make many herbal drugs and plant extracts more effective. This is because some of them don't dissolve well in fats (lipid soluble), making them less effective in our bodies [3].

Even though some herbal drugs show great potential in laboratory tests (in-vitro), they often

don't work as well inside our bodies (in-vivo). This is because they struggle to dissolve in fatsor are the wrong size, leading to poor absorption and effectiveness.

When we extract substances from plants, different components work together (synergistic action), and separating them can reduce their specific activity. The complexity of the extract's chemicals seems to play a crucial role in how well the active components work.[4]

A big challenge is that many plant components, especially phenolics, dissolve in water but struggle to cross the fatty membranes of our intestines. To solve this, scientists are exploring new delivery systems like liposomes, marinosomes, niosomes, and lipid-based systems. These systems help release the substances more effectively and allow them to cross the fatty membranes in our bodies [5].

One exciting discovery is that drug delivery systems based on phospholipids show promise in delivering herbal drugs effectively. The key to the success of any herbal product is making sureit delivers an effective amount of the active compounds [6].

Plant Profile:

1. **Bacopa Monnieri: [7]**

Plant Name: Bacopa Monnieri

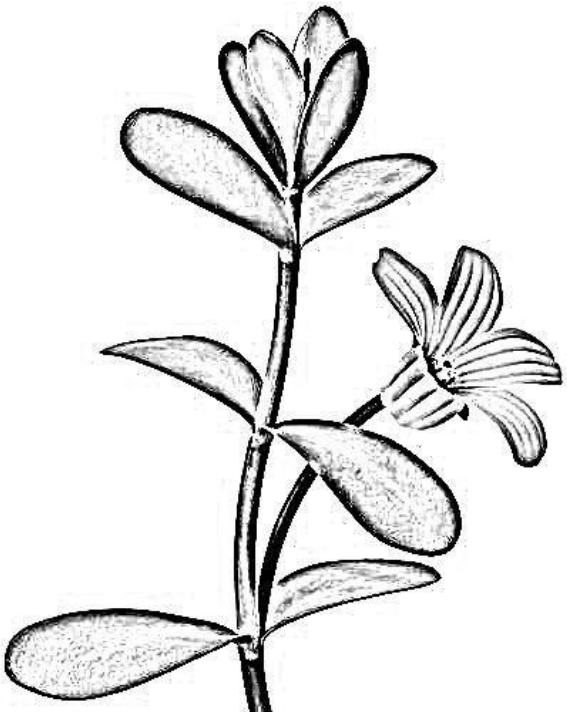

Figure 1 Bacopa Monnieri PlantSynonyms: Brahmi, Water Hyssop, Thyme-leafed Gratiola

Biological Source: Bacopa Monnieri is a perennial herb that thrives in wetlands, native to regions of Asia, particularly India and Nepal.

Chemical Constituents: Bacopa Monnieri boasts a diverse array of chemical constituents,

including bacosides, alkaloids, flavonoids, and saponins. These compounds contribute to its adaptogenic and cognitive-enhancing properties.

Uses: Traditionally, Bacopa Monnieri has been utilized in Ayurvedic medicine for its adaptogenic qualities, aiding in stress management. Recent research explores its potential to enhance memory and cognitive function, making it a valuable herb in the realms of mental well-being.

2. Moringa oleifera: [8]

Plant Name: Moringa oleifera

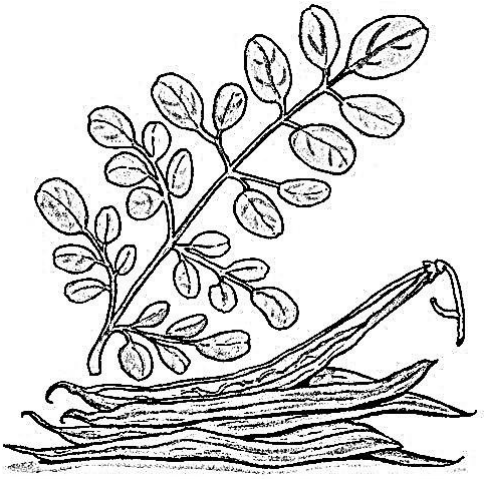

Figure 2 Moringa oleifera Leaf and PodsSynonyms: Drumstick tree, Miracle tree, Ben oil tree

Biological Source: Moringa oleifera, commonly referred to as the Miracle Tree, is a fast-growing deciduous tree native to parts of Africa, Asia, and the Indian subcontinent.

Chemical Constituents: Moringa oleifera is a treasure trove of nutrients, containing vitamins (such as vitamin C, A, and B), minerals (including calcium, potassium, and iron), antioxidants like quercetin and chlorogenic acid, and various amino acids.

Uses: The uses of Moringa oleifera are diverse; its leaves and pods are edible, providing essential nutrients. In traditional medicine, it has been recognized for its anti-inflammatory, antioxidant, and antimicrobial properties. Additionally, Moringa oleifera has found applications in water purification due to its coagulant properties, further showcasing itsversatility.

2. Concept of bioavailability enhancers

The idea of 'bioavailability enhancers' originates from the ancient Ayurvedic system, a traditional science of life. In Ayurveda, black pepper, long pepper, and ginger are collectively referred to as "Trikatu," where "Trikatu" translates to three acrids in Sanskrit. The understanding of bioenhancers was initially recorded by Bose in 1929. Bose documented the impact of long pepper, stating that it enhanced the antiasthmatic properties of Adhatoda vasika leaves. This revelation marked an early acknowledgment of the synergistic actions within

traditional Ayurvedic components.

Table 1: Examples of Herbal Bioenhancers

Herbal Bioenhancer	Source	Enhanced Compounds
Piperine	Black pepper	Curcumin, resveratrol
Quercetin	Onions, apples	Resveratrol, catechins
Gingerol	Ginger	Curcumin, quercetin
Bioperine	Black pepper extract	Various nutrients
Rutin	Buckwheat, citrus	Quercetin, resveratrol

Table 2: Bioenhancement Effects of Herbal Bioenhancers

Herbal Bioenhancer	Bio enhancement Effects
Piperine	Increases absorption of curcumin and resveratrol
Quercetin	Enhances absorption of resveratrol and catechins
Gingerol	Improves bioavailability of curcumin and quercetin
Bioperine	Enhances absorption of various nutrients and herbal extracts
Rutin	Boosts bioavailability of quercetin and resveratrol

Table 3: Potential Applications of Herbal Bioenhancers

Herbal Bioenhancer	Potential Applications
Piperine	Nutritional supplements, functional foods
Quercetin	Antioxidant formulations, herbal extracts
Gingerol	Joint health supplements, anti-inflammatory products
Bioperine	Multivitamins, herbal remedies
Rutin	Cardiovascular health products, antioxidant blends

3. Definition and history of bioavailability enhancers

'Bioavailability enhancers' act as facilitators for drugs, comprising molecules that, on their own, don't exhibit typical drug activity. However, when used in combination, these enhancers boost the activity of drug molecules in various ways. This includes increasing the bioavailability of

the drug across membranes, enhancing drug potency through conformational interactions, acting as receptors for the drug molecule, and making target cells more receptive to drugs. A 'bioenhancer' specifically refers to an agent capable of enhancing the bioavailability and bioefficacy of a particular drug it is combined with, without possessing typical pharmacological activity at the used dose.

These enhancers are also known as 'absorption enhancers,' functional excipients included in formulations to improve the absorption of pharmacologically active drugs. The term 'bioavailability enhancer' was coined by Indian scientists at the Regional Research Laboratory, Jammu (now the Indian Institute of Integrative Medicine, Jammu). They scientifically validated piperine as the world's first bioavailability enhancer in 1979.

C.K. Atal, the Director of the institute, noticed that a majority of ancient Indian Ayurvedic formulations used in treating various diseases contained either Trikatu or one of its ingredients, Piper longum. Trikatu consists of black pepper (Piper nigrum), long pepper (P. longum), and ginger (Zingiber officinale). Based on this observation, they studied these ingredients and found that Piper longum, specifically piperine, increased the bioavailability of many drugs. Piperine was isolated, and its bioavailability-enhancing action was established. Subsequent research demonstrated its effectiveness across various drug classes, including antitubercular, leprosy, antibiotics, non-steroidal anti-inflammatory drugs, cardiovascular, and central nervous system drugs. Piperine was shown to increase the bioavailability of different drugs by 30% to 200%. However, it was noted that piperine did not uniformly increase the bioavailability of all drugs, with inconsistent effects observed in some cases [9].

4. Drug absorption obstacles

For a drug to exert its biological effects, it must traverse the epithelial barrier of the intestinal mucosa, moving from the gut's lumen into the systemic circulation. However, various anatomical and biological obstacles impede the penetration of the oral drug delivery system through the epithelial membrane[10].

Numerous structures within the intestinal epithelium act as barriers to drug transfer from the gastrointestinal tract to the systemic circulation. One such potential hindrance is an aqueous stagnant layer, owing to its hydrophilic nature, acting as a barrier to drug absorption[11]. Drug molecules larger than approximately 0.4 nm encounter difficulty passing through these aqueous channels[12].

Recent studies reveal that drug efflux pumps, notably P-glycoprotein, play a crucial role in impeding efficient drug entry into the systemic circulation[11]. P-glycoprotein, an ATPase and energy-dependent transmembrane drug efflux pump belonging to the ABC transporter family, has a molecular weight of approximately 170 kDa and comprises 1,280 amino acid residues[13].

Methods for Enhancement of Bioavailability of Orally Administered Drugs:

5.1. Absorption Enhancers:

Several absorption enhancers effectively improve intestinal absorption, including bile salts, surfactants, fatty acids, chelating agents, salicylates, and polymers [13],[14]. Trimethylated chitosan, particularly chitosan, enhances drug absorption via the paracellular route by

redistributing cytoskeletal F-actin, causing the opening of tight junctions. Surfactants such as bile, bile salts, and fatty acids act as absorption enhancers by increasing the solubility of hydrophobic drugs in the aqueous layer or by enhancing the fluidity of apical and basolateral membranes. Calcium chelators like ethylene glycol tetraacetic acid and ethylene diamine tetraacetic acid (EDTA) improve absorption by reducing extracellular calcium concentration, leading to the disruption of cell-cell contacts [14].

5.2. Prodrugs:

Prodrugs, such as various ampicillin derivatives, exemplify enhancing the lipophilicity of agents to improve the absorption of a polar drug through prodrug strategy[15]. For instance, ampicillin, being hydrophilic, is only 30%-40% absorbed from the gastrointestinal tract. Prodrugs like pivampicilline, bacampicilln, and talampicillin are synthesized by esterifying the carboxyl group of ampicillins.

5.3. Dosage Form and Other Pharmaceutical Approaches:

Various dosage formulations, such as liposomes and emulsions, enhance the intestinal absorption of insoluble drugs [16] Techniques like particle size reduction throughmicronization, nanoparticular carriers, complexation, and liquid crystalline phases are employed to maximize drug absorption [17],[18].

5.4. P-glycoprotein Inhibitors:

P-glycoprotein inhibitors aim to reverse P-glycoprotein-mediated efflux, enhancing the efficiency of drug transport across the epithelial membrane. These inhibitors influence the metabolism, absorption, distribution, and elimination of P-glycoprotein substrates, thereby modulating pharmacokinetics [19].

6. Mechanism of action of bioenhancers of herbal origin

Herbal bioenhancers employ various mechanisms to enhance their actions, and different ones may operate through similar or distinct pathways. Nutritional bioenhancers boost absorption by interacting with the gastrointestinal tract, while antimicrobial bioenhancers primarily influence drug metabolism processes.

Several mechanisms have been proposed for herbal bioenhancers, including:

Reduction in Hydrochloric Acid Secretion and Increased Gastrointestinal Blood Supply: This mechanism can impact the absorption process [20].

Inhibition of Gastrointestinal Transit, Gastric Emptying Time, and Intestinal Motility: These actions may affect the rate at which drugs are absorbed [21],[22].

Modifications in GIT Epithelial Cell Membrane Permeability: Changes in permeability can influence drug absorption [23],[24].

Cholagogous Effect: This effect relates to the stimulation of bile secretion [25].

Bioenergetics and Thermogenic Properties: These properties can contribute to the overall enhancement of bioavailability [26],[27].

Suppression of First Pass Metabolism and Inhibition of Drug Metabolizing Enzymes: These actions can influence drug metabolism and bioavailability [27].

Stimulation of Gamma Glutamyl Transpeptidase (GGT) Activity: This stimulation enhances the uptake of amino acids [28].

Mechanism of Action of Piperine (a Herbal Bioenhancer):

Piperine, a prominent herbal bioenhancer, employs various mechanisms for its bioenhancer activity:

DNA Receptor Binding: Piperine has been suggested to bind to DNA receptors.

Modulation of Cell Signal Transduction: It influences the transmission of signals within cells.

Inhibition of Drug Efflux Pump: Piperine can inhibit pumps responsible for removing drugs from cells [29].

In general, piperine inhibits drug-metabolizing enzymes, stimulates amino acid transporters in the gut, inhibits cell pumps responsible for drug elimination, and inhibits the intestinal production of glucuronic acid. It may enhance drug absorption in the gastrointestinal tract or inhibit enzymes responsible for drug metabolism, particularly in the liver after the drug's absorption from the GIT.

Studies have shown that piperine inhibits hepatic arylhydrocarbon hydroxylase and UDP-glucuronyltransferase activities, key enzymes in drug metabolism. Additionally, piperine modifies the rate of glucuronidation by lowering endogenous UDP-glucuronic acid content and inhibiting transferase activity.

Piperine inhibits human P-glycoprotein and cytochrome P450 3A4 (CYP3A4), both of which significantly contribute to the first-pass elimination of many drugs [32]. It affects various metabolizing enzymes, including CYP1A1, CYP1B1, CYP1B2, CYP2E1, and CYP3A4, influencing drugs metabolized by these enzymes. Other suggested mechanisms of action include making target receptors more responsive to drugs, acting as receptors for drug molecules, increasing GIT vasculature by vasodilation to enhance drug absorption, and modulating cell membrane dynamics to facilitate drug transport across cell membranes [31].

7. Necessary of Bioavailability Enhancers

The ability of molecules to pass biological membranes and be systematically absorbed, whether through oral or topical administration, is significantly influenced by two key factors: lipid solubility and molecular size.

Despite showcasing excellent bioactivity in laboratory settings, several plant extracts and phytoconstituents often fall short in demonstrating the same effectiveness in vivo. This discrepancy is primarily attributed to their poor lipid solubility or inappropriate molecular size, or sometimes, a combination of both. The consequence is a suboptimal absorption rate,leading to poor bioavailability. Notably, when individual constituents are isolated from a plant extract, there is often a loss of specific bioactivity. Moreover, some constituents withinmulti-constituent plant extracts may face degradation in the stomach's acidic environment when taken orally.

The use of these plant extracts can offer notable advantages. They not only contribute to dose economy but also reduce the treatment duration, thereby minimizing drug resistance issues. This approach proves to be cost-effective, as it lowers treatment expenses, while concurrently mitigating drug toxicity and adverse reactions. In essence, the strategic utilization of plant extracts aligns with the goal of optimizing therapeutic outcomes in a safeand efficient manner.

8. Problems with Bioenhancers

Despite the success of bioenhancers in drug delivery, it's important to acknowledge that notall approaches have yielded the same level of success. The development of new bioenhancers

brings along specific challenges that require careful consideration and resolution. Researchers are actively addressing these challenges by modifying the physicochemical characteristics of nanomaterials to enhance properties such as prolonged circulation in the blood, increased functional surface area, protection of incorporated drugs from degradation, overcoming biological barriers, and achieving site-specific targeting.

One significant challenge in the research and development of herbal bioenhancers is the issue of large-scale production. While successful at the laboratory or pilot scale, there's a critical need to scale up these technologies for eventual commercialization. Challenges associated with scaling up include dealing with low concentrations of nanomaterials, preventing agglomeration, and addressing the complexities of the chemical processes. Modifying nanomaterials at the laboratory scale for improved performance is often more straightforward than doing so on a larger scale. Maintaining the size and composition of nanomaterials that enhance bioavailability poses a particular challenge in large-scale production.

Moreover, as advancements in herbal bioenhancers continue, they introduce new challenges for regulatory control. There's a growing need for regulations that account for the unique physicochemical and pharmacokinetic properties of nano drug products, which differ from conventional drug products. Regulatory bodies like the United States' Food and Drug Administration and the European Medicines Evaluation Agency are proactively addressing these challenges and identifying possible scientific and regulatory issues associated with the evolving field of herbal bioenhancers [34].

9. Future Prospectus of Herbal Bioenhancers

The utilization of bioenhancers in drug delivery not only leads to a reduction in dosage but also serves to minimize the risks associated with drug resistance. The lowered dosage contributes to a decrease in drug toxicity, a particularly significant advantage observed in the case of potent anticancer drugs like taxol.

Taxol, commonly used in the treatment of ovarian and breast cancer, is derived from the bark of the Pacific yew tree, known for being one of the slowest-growing trees globally. Traditionally, to treat a single patient, the extraction of taxol required the felling of six trees, each aged between 25 to 100 years. However, with the incorporation of bioenhancers, the need for such extensive destruction is mitigated.

This not only enhances the ecological sustainability of the treatment but also reflects a more conscientious approach towards the environment. The reduction in the number of trees required for drug extraction aligns with a more environmentally friendly and sustainable approach to pharmaceutical production. In this way, the integration of bioenhancers not only benefits patient health but also contributes positively to broader ecological concerns.

10. Role of Natural Compounds from Medicinal Plants as Drug Bioavailability Enhancers

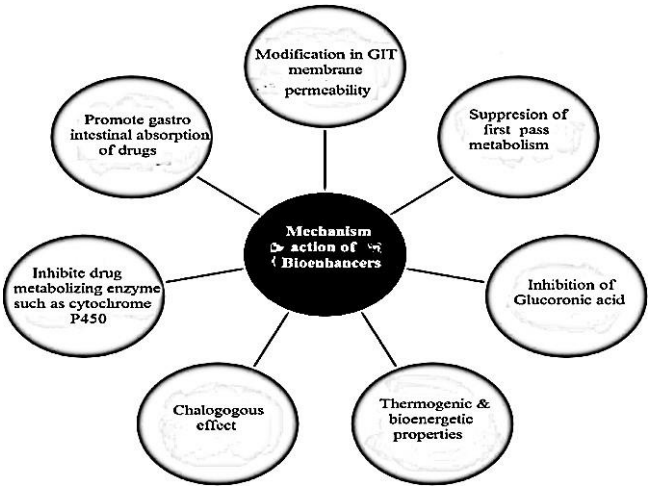

Figure 3 Mechanism of Herbal Bioenhancer

10.1. Glycyrrhizin

Found in Glycyrrhiza glabra, glycyrrhizin exhibits potent absorption-enhancing activity, surpassing caproic acid.

10.2. Genistein

As an isoflavone, genistein inhibits efflux functions like P-glycoprotein, significantlyboosting the absorption of drugs like paclitaxel.

10.3. Lysergol

Isolated from plants like Rivea corymbosa, lysergol enhances antibiotic activity against bacteria.

10.4. Zingiber officinale

Ginger regulates the intestinal function, increasing the bioavailability of antibiotics like azithromycin and amoxycillin.

10.5. Naringin

Abundant in grapefruit, naringin enhances the absorption of drugs like paclitaxel,showcasing antioxidant and anticarcinogenic properties.

10.6. Quercetin

Quercetin, a flavonoid found in citrus fruits, boasts antioxidant, anti-inflammatory, and anti-tumoral effects. It enhances the bioavailability of drugs like diltiazem and digoxin.

10.7. Sinomenine

Derived from Sinomenium acutum, sinomenine dramatically increases the bioavailability of paeoniflorin, a treatment for inflammation.

10.8. Cuminum cyminum Linn.

Cuminum cyminum Linn., a herb, exhibits bioavailability/bioefficacy enhancing activity attributed to volatile oils and flavonoids.

10.9. Allium sativum

Allicin in garlic enhances the fungicidal activity of amphotericin B against fungi.

10.10. Aloe vera

Aloe vera improves the absorption of vitamins C and E, showcasing potential as a nutritional herbal bioenhancer.

10.11. Nitrile Glycosides

Derived from Moringa oleifera, nitrile glycosides promote drug absorption, enhancing antibiotics and vitamins.11. Various Lipid Technologies for Enhancing Bioavailability

Lipid technologies like liposomes, microspheres, nanoparticles, transferosomes, ethosomes, and lipid-based systems play a crucial role in enhancing bioavailability, offering diverse options for drug delivery from herbal sources.

10.12. Bacopa Monnieri

Bacopa Monnieri, known for its cognitive-enhancing properties, acts as a bioenhancer by improving the absorption of drugs, contributing to enhanced therapeutic effects.

10.13. Moringa oleifera

Moringa oleifera, rich in nitrile glycosides, serves as a bioenhancer by promoting the absorption of drugs. It demonstrates efficacy in enhancing the bioavailability of antibiotics and vitamins, contributing to improved therapeutic outcomes.

References:

1. Veiga F, Fernandes C, Teixeira F. Oral bioavailability and hypoglycemic activity of tolbutamide/cyclodextrin inclusion complexes. Int J Pharm. 2000;202:165–171.
2. Varma MV, Ashokraj Y, Dey CS, Panchagnula R. P-glycoprotein inhibitors and theirscreening: a perspective from bioavailability enhancement. Pharmacol Res. 2003;48:347–359.
3. Annamalai AR, Manavalan R. Effects of Trikatu and its individual components andpiperine on gastrointestinal tracts: Trikatu as a bioavailability enhancer. Ind Drugs.1989;27(12):595–604.
4. 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.
5. Majeed M, Badmaev V, Rajendran R. Use of piperine to increase the bioavailability of nutritional compounds. 1995 United States Patent, Number 5536506.
6. Khajuria A, Thusu N, Zutshi U. Piperine modulates permeability characteristics of the intestine by inducing alterations in membrane dynamics: influence on brush border membrane fluidity, ultrastructure, and enzyme kinetics. Phytomed. 2002;9:224–231.
7. Firoj A. Tamboli1, Vinod D. Rangari, Shreyash D. Tarlekar, Rajendra D. Jadhav,Kamal M. Alaskar4, Vaibhava V. Desai4, Rajesh U. Kanthe, “Brahmi (Bacopa monnieri): an ayurvedic herb in the management of various diseases ”Journal of Postharvest Technology 2022, 10(4): 59-74.
8. Attilio Anzano, Attilio Anzano, ScilitPreprints, View Publications, MohammadAmmar, Marina Papaianni, Laura Grauso, Mohammed Sabbah, Rosanna Capparelli andVirginia Lanzotti, “Moringa oleifera Lam.: A Phytochemical andPharmacological Overview” Horticulturae 2021, 7(10), 409;
https://doi.org/10.3390/horticulturae7100409
9. Reanmongkol W, Janthasoot W, Wattanatorn W, Upakorn PD, Chudapongse P. Effects of Piperine on bioenergetics functions of isolated rat liver mitochondria. Biochem Pharmacol. 1988;37:753–757.

10. 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 Therap. 1985;232:258–262.
11. 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. Biochem Pharmacol. 1992;43:1401–1407.
12. Kandalkar, A., Bhise, M., Chandurkar, P., Vasu, S., Pahuja, S., Patond, V., & Mohapatra, S. Effect of permeation enhancer on bioavailability of formulated
patches of amoxicillin. International Journal of Health Sciences, (II), 12951-12965.
13. Bajad S, Bedi KL, Singla AK, Johri RK. Piperine inhibits gastric emptying and gastrointestinal transit in rats and mice. Planta Med. 2001;67:176–179.
14. 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;232:258–262.
15. 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 endogenous UDP-glucuronic acid content. J Pharmacol Exp Ther. 2002;302:645–650.
16. 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. JPharmacol Exp Ther. 2002;302:645–650.
17. Khajuria A, Zutshi U, Bedi KL. Permeability characteristics of piperine on oral absorption - An active alkaloid from peppers and a bioavailability enhancer. Ind J Exp Biol. 1998;36:46–50.
18. Ashish Kandalkar, Nilesh Chachda, Somkant Jawarkar, Ansar Patel, Harshada Wagh, Shubham Gore, Shreyas Kulkarni, Rakesh Dhole “Formulation And Development Of Transdermal Patches Of Amoxicillin And Comparative Effect Of Natural Permeation Enhancers On Ex Vivo Release”, Journal of Namibian Studies,35 S1 (2023): 2681-2697.
19. Wagner V, Dullaart A, Bock A-K, Zweck A. The emerging nanomedicine landscape.Nat Biotech. 2006;24(10):1211–1217.
20. 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 Nutr. 2001;74:418–425.
21. Hoi JS, Li X. Enhanced diltiazem bioavailability after oral administration of diltiazem with quercetin to rabbits. Int J Pharm. 2005;297:1–8.
22. Dupuy J, Larrieu G, Sutra JF, Lespine A, Alvinerie M. Enhancement of moxidectin bioavailability in lamb by a natural flavonoid: quercetin. Vet Parasitol. 2003;112:337–347.
23. Wang YH, Chao PD, Hsiu SL, Wen KC, Hou YC. Lethal quercetin-digoxin interaction in pigs. Life Sci. 2004;74:1191–1197.
24. Kandalkar, A., Dhole, R., Jawarkar, S., Patel, A., Pawar, D., Wagh, H., ... & More,
S. (2023). Transdermal Telmisartan Patch Development With Natural Permeation Enhancers: Ex Vivo Release Comparison. Journal of Namibian Studies: History Politics Culture, 35, 3504-3523.
25. 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. 2005. p. p. 89. Boston: 2nd International Conference on Tumor Progression & Therapeutic Resistance Proceedings.

26. Pichard LG, Gillet G, Fabre I, Dalet-Beluche I, Bonfils C, Thenot JP. Identificationof the rabbit and human cytochromes P-450IIIA as the major enzymes involved in the N-demethylation of diltiazem. Drug Metab Dispos. 1991;18:711–719.
27. Molden E, Asberg A, Christensen H. Desacetyl-diltiazem displays several fold higher affinity to CYP2D6 compared with CYP3A4. Drug Metab Dispos. 2002;30:1–3.
28. Kandalkar A, Singh N. Effect of permeation enhancer on bioavailability of formulated patches of glibenclamide. Int J Pharm Investig. 2021;11(2):214-9. doi: 10.5530/ijpi.2021.2.38.
29. Dr. Sanjay Vasu Dr. Ashish Kandalkar, Dr. Nitu Singh "Natural permiation Extract for Transdermal Drug Delivery System" Indian Patent No. 202121019913
30. Flavonoid dimers as bivalent modulators for p-glycoprotein-based multidrug resistance: structure-activity relationships.
31. Chan KF, Zhao Y, Chow TW, Yan CS, Ma DL, Burkett BA, Wong IL, Chow LM, Chan TH. ChemMedChem. 2009 Apr;4(4):594-614. doi: 10.1002/cmdc.200800413.