different techniques of reducing particle size such as nanoparticle creation, micronization, and complexation assist in the absorption of insoluble drugs or can increase the absorption rate [7,8].

Inhibiting the P-glycoprotein

These are some absorption barriers present on the gastrointestinal tract (GIT) epithelial layer; by inhibiting these barriers, the absorption rate can increase to an excellent extent. P-glycoprotein inhibitors influence the metabolism, absorption, distribution, and elimination of P-glycoprotein substrates in the process of modulating pharmacokinetics [9].

Mechanism of bioenhancers

Some of the mechanisms of action of bio-enhancers are:

a. Decrease in the secretion of hydrochloric acid and an increase in gastrointestinal blood supply [10],
b. Increasing the stay of what we eat in the GIT so that it has more time to get absorbed. By decreasing the intestinal motility and enhancing the time of stomach emptying [11,12],
c. Modifications in GIT epithelial cell membrane permeability [13,14],
d. Cholagogous effect (increased bile secretion) [13],
e. Bioenergetics and thermogenic properties [13,15] and
f. Stopping the first-pass metabolism, metabolizing enzymes inhibition, and stimulation of gamma-glutamyl transpeptidase activity, intensify the uptake of amino acids [15,16].

For example, mechanism of action of piperine: DNA receptor binding, modulation of cell signal transduction and inhibition of drug efflux pump, etc. [11].

Classification

Based on origin bio-enhancers can be classified as

1. Herbal origin: They are derived from natural sources, for example, piperine, curcumin, ginger, and caraway .
2. Non-herbal origin: These are bio-enhancers, which are not, obtained from plants but by some synthetic modification of other natural sources, for example, Capmul that is mono-, di- and triglyceride, formulated by the glycerolysis of selected fats, vegetable oils or by glycerin esterification with particular fatty acids; and cow urine distillate [17,18].

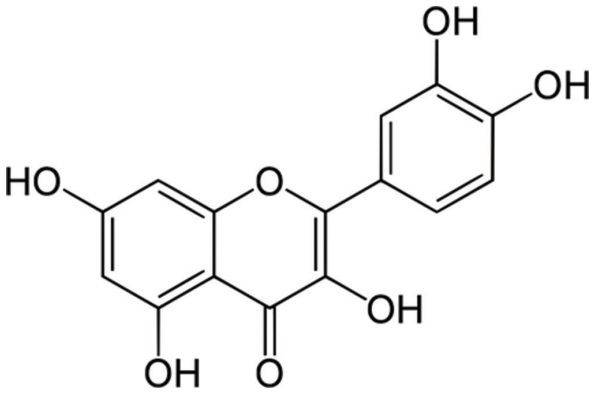
Based on mode of toxic action (MOA) – based on MOA classification is as follows

1. Inhibitors of PGPefflux pump: Caraway, quercetin, naringin, and cumin.
2. Suppressor of CYP 450 enzyme and its isoenzymes: Gallic acid and its esters.
3. Regulate GIT absorption: Aloe vera, glycyrrhiza, etc. [19].

Natural product used as bioavailability enhancers

Quercetin

It is an aglycone form of several flavonoid glycosides found in various citrus fruits. The chemical structure consisting of a chromene ring with a dihydroxy phenol.



IUPAC name: 2-(3, 4-dihydroxyphenyl)-3, 5, 7-trihydroxy-4H-chromen-4-one

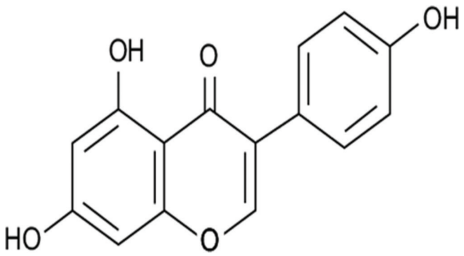
A considerable amount of it is found in apples, raspberries, honey, cherries, onions, red grapes, citrus fruits, green leafy vegetables, etc. Among vegetables and fruits, quercetin content is highest in onions [20]. The wide range of beneficial biological activities shown by quercetin includes antioxidant, radical scavenging, anti-inflammatory, anti-atherosclerotic, anti-tumoral, and anti-viral effects [21]. The different examples of drugs such as diltiazem, digoxin, and epigallocatechin gallate had shown a rise in bioavailability, blood levels, and efficacy when used in combination with quercetin [22].

Various preclinical trials showed the ability of quercetin to enhance bioavailability. A preclinical test done on rabbits with diltiazem indicated that the area under the plasma concentration-time curve (area under curve [AUC]) and peak concentration (Cmax) of diltiazem in the quercetin pretreated rabbits were notably higher than those acquired from the groups not treated with quercetin. Various studies describe that diltiazem is metabolized both in the liver and small intestine by CYP3A4. The P-glycoprotein efflux pump prevents the absorption of diltiazem through the mucosa of the intestine. The rise in AUC and Cmax of diltiazem by pretreatment of quercetin might have caused by the inhibition of the P-glycoprotein efflux pump and the metabolizing enzyme CYP3A4 in the intestinal mucosa [23,24].

The reported results are: The absorption of epigallocatechin gallate reported to be enhanced with red onion supplementation, abundant source of quercetin. For 6 h, the AUC of epigallocatechin gallate was increased from 1323 to 1814 ng/mL, when administered along with quercetin. When quercetin was taken along with epigallocatechin gallate, it results in an increased absorption of epigallocatechin gallate from the intestine [25]. The increased bioavailability of moxidectin in lambs was observed due to natural flavonoid quercetin. It was found in various studies that, quercetin was able to modify the pharmacokinetics of moxidectin in plasma of lambs [22]. Oral bioavailability of rivastigmine increased with quercetin nanoparticles due to inhibition of CYP3A4 and esterases [26].

Genistein

It belongs to the isoflavone class of flavonoids and a phytoestrogen. It is found in numerous plants including lupin, soybeans, fava beans, kudzu, and psoralea being the essential food source, likewise in the medicinal plants, *Flemingia vestita* and *Flemingia macrophylla*, and coffee [27]. It consists of a chromene ring.



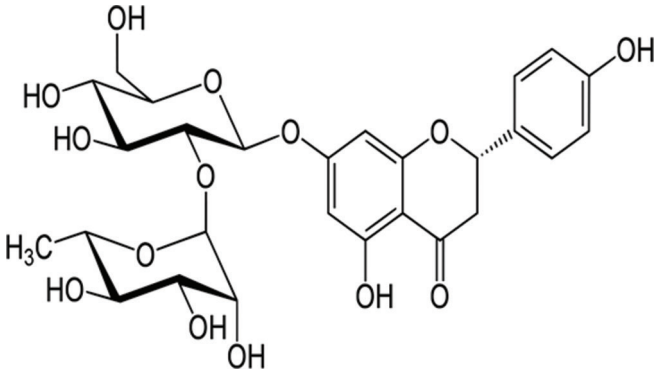
IUPAC name: 5,7-Dihydroxy-3-(4-hydroxyphenyl)chromen-4-one

According to reports, it can inhibit P-glycoprotein, breast cancer resistance protein (BCRP) and multidrug resistance-associated protein 2 (MRP2) efflux function, the intestinal absorption of paclitaxel (a substrate for efflux transports such as P-glycoprotein, BCRP and MRP2) increases dramatically, when co-administered with genistein [28-30]. The contributor in the improvement of systemic exposure of paclitaxel is the inhibition of the efflux transporters caused by genistein. 10 mg/kg of genistein caused enlargement of 54.7% in AUC and a decline of 35.2% in the total plasma clearance after oral administration of paclitaxel at an amount of 30 mg/kg in rats [30].

Naringin

It is a natural bio-enhancer obtained from citrus fruits, especially in grapefruit. Naringin is responsible for the fruit's bitter taste. The

chemical structure consist of a flavone-7-O-glycoside between the flavanone naringenin and the disaccharide neohesperidose [31].



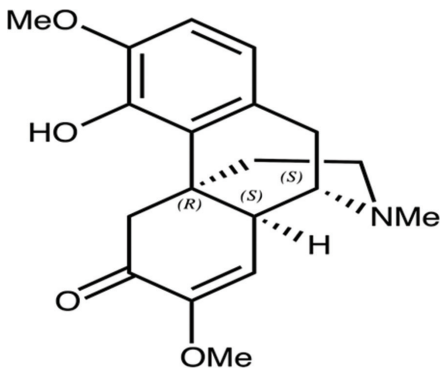
IUPAC name: 7-[[2-*O*-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]-2,3-dihydro-5-hydroxy-2-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one

The various pharmacological effects shown by naringin include antioxidant, blood lipid-lowering, and anticarcinogenic activities. In multiple studies done on rats its observed that naringin also inhibits CYP3A1/2 and P-glycoprotein. When naringin of doses 3.3 and 10.0 mg/kg was given orally 30 min before the intravenous administration of 3 mg/kg dose of paclitaxel, a remarkable rise of 40.8% and 49.1% in AUC for both naringin doses, respectively, was reported after the intravenous administration of paclitaxel [31].

Sinomenine

Sinomenine is an alkaloid extracted from *Sinomenium acutum* Thunb.

Its structure and IUPAC [32].

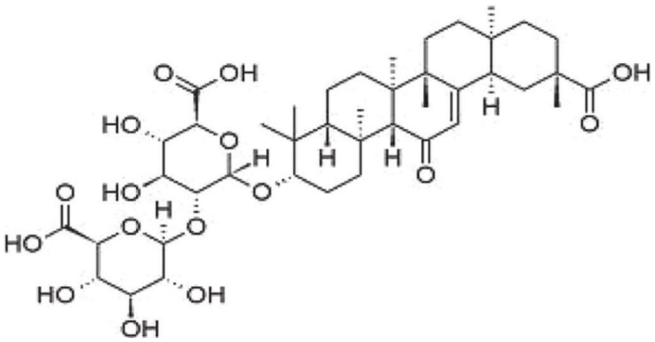


IUPAC name (9α, 13α, 14α)-4-Hydroxy-3, 7-dimethoxy-17-methyl-7, 8-didehydromorphinan-6-one

Paeoniflorin is a bioactive monoterpene glycoside, used widely to treat inflammation and arthritic conditions. The problem with paeoniflorin is that its absorption rate is weak, and hence bioavailability is low. Its bioavailability is around 3–4% when administered orally. When paeoniflorin and sinomenine are co-administered, the pharmacokinetic behaviors of paeoniflorin are altered dramatically in rats, which resulted in increased oral bioavailability of paeoniflorin by more than 12 times. The reason behind this enhanced bioavailability by sinomenine could be the decrease in the efflux transport of paeoniflorin by P-glycoprotein in the small intestine [33-35].

Glycyrrhizin

It is a triterpenoid saponin found in *Glycyrrhiza glabra* L. belonging to family Fabaceae). The chemical structure of glycyrrhizin with its IUPAC name.



IUPAC (3β,20β)-20-carboxy-11-oxo-30-norolean-12-en-3-yl 2-O-β-D-glucopyranuronosyl-α-D-glucopyranosiduronic acid

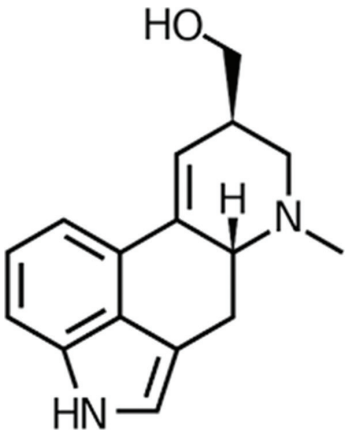
Absorption enhancing activity by glycyrrhizin found more effective than caproic acid when both tested at the same concentration [36]. The absorption-increasing property in Caco-2 cell monolayer was found considerably more from sodium deoxycholate and dipotassium-glycyrrhizin treatment done simultaneously than sodium deoxycholate alone [37].

Nitrile glycosides

The biological source of nitrile glycosides and its derivatives consist of the pods of *Moringa oleifera*, belonging to family moringaceae. As observed in various studies, they do not have their drug activity but can promote and raise the biological activity, bioavailability of the drug uptake in combination therapy. The nitrile glycoside, like niaziridin, has enhanced the absorption of vitamins, nutrients, and various commonly used antibiotics such as ampicillin, rifampicin, and tetracycline . In a bioactivity test, the activity of ampicillin, rifampicin, and nalidixic acid against both Gram- positive and Gram-negative strains was notably improved, by the niaziridin-rich fraction of *M. oleifera* [38].

Lysergol

It is an alkaloid found in some species of fungi like ergot fungus and in the morning glory family of plants (Convolvulaceae), which include the hallucinogenic seeds of *Rivea corymbosa*, *Argyreia nervosa*, and *Ipomoea violacea*. As it is a derivative of dimethylergoline, also called clavine. The four-ring structure of lysergol and its IUPAC name.



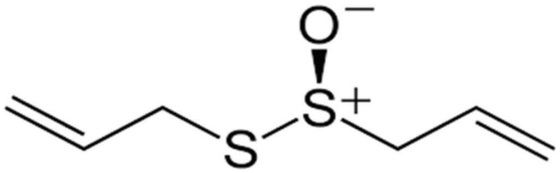
IUPAC name (7-Methyl-4,6,6a,7,8,9-hexahydro-indolo [4,3-fg] quinolin-9-yl)-methanol

It is an excellent herbal bio-enhancer, as it amplifies the killing activities of different antibiotics on bacteria [39].

Allium sativum

Allicin is the active bio-enhancer found in garlic. It enhances the fungicidal activity of amphotericin B against pathogenic fungi such as *Candida albicans*, *Aspergillus fumigatus*, and yeast (*Saccharomyces*

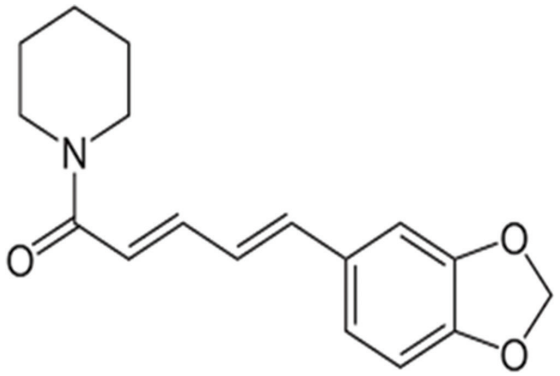
cerevisiae) [40]. Allicin is an acyclic compound with a straight-chain having sulfur as its constituent.



IUPAC *S*-Prop-2-en-1-yl prop-2-ene-1-sulfinothioate

Piperine

It is a well-known alkaloid obtained from *P. nigrum* or *P. longum*, whether stem, pods, or leaf parts. It has proved to be a milestone in the field of biopotentiation. It is authorized as safe by FDA [41]. It contains a cyclic six-membered secondary amine in its structure as follows.



IUPAC name: (2*E*,4*E*)-5-(2*H*-1,3-Benzodioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one

The use of piperine in different formulations

Metabolic enzymes

Piperine has shown its effect on metabolic enzymes and degradation related enzymes both *in vitro* and *in vivo*. It has been proved as a non-specific inhibitor of drug metabolism in different studies. There are various series of enzymes inhibited by piperine, mainly associated with P-GP and cytochrome P 450 families [15,42]. It also includes others such as:

a. Aryl hydrocarbon hydroxylase (of Microsomal enzyme system)
b. Ethyl morphine-N demethylase
c. 7-Ethoxycoumarin-O-de-ethylase
d. Uridine diphosphate glucose dehydrogenase
e. Uridine diphosphate glucose dehydrogenase
f. Uridine diphosphate glucuronyltransferase
g. 5-Lipoxegenase (h) Cyclo-oxygenase-I.

Antitubercular and antileprotic drugs

Bioenhancing property of piperine utilized first to treat tuberculosis in humans, for example, alongside Rifampin or Rifampicin (the medication of first-line therapy in tuberculosis and leprosy). It extend the bioavailability of rifampicin by about 60%, and subsequently reduced the dose from 450 to 200 mg. Rifampin works by acting on RNA polymerase and inhibits the transcription of the polymerase in human cells, which is being catalyzed by *Mycobacterium smegmatis*. Piperine enhances this activity of rifampin by several folds against RNA polymerase Piperine also stimulates the coupling capacity of rifampin to RNA polymerase even in resistant strains [43,44].

Antibiotics

There has been a considerable increment in the consumption of antibiotics and antimicrobials at a very high rate, which has caused most of the cases such as immune system resistance or addiction. Patients require a high dose of such drugs due to reduced GIT absorption, uptake by pathogens, and cells that have decreased due to resisting efflux pumps. The large part of the target dose remains as waste in body fluids having no remedial use but causing drug resistance and side effects or toxicity with time. In the studies done on rabbits, fluoroquinolones and piperine have shown raised bioavailability as piperine inhibits the P-glycoprotein efflux pump [45].

Chemoprevention and immunomodulators

Piperine decreases cytotoxicity by reducing aflatoxins, which causes cytotoxicity by inhibiting CYP-P450-mediated biological activation of mycotoxins into harmful ones [46]. It modifies the oxidative changes in cells by inhibiting the lipid peroxidation phenomena, resulting in free radicals scavenging activity [47]. This process diminishes the harm to DNA and DNA proteins. The antiapoptotic property of piperine is due to the induction of Heme-oxygenase-1. It contains the pentacyclic oxindole group in it, responsible for all these activities [48].

Nutraceuticals

It likewise enhances bioavailability and retention of nutrients by acting on the alimentary canal, acting as a nutritional bio-enhancer. During double-blind cross over studies, the increase in the concentration of vitamins against placebo by 50–60% utilizing herbal supplementation was revealed. The outcome from various studies expresses that it is because of the nonspecific mechanism and thermogenic properties of piperine [12,49].

Other upgraded bioavailability showed by it of medications like Nevirapine, a potent non-nucleoside inhibitor of HIV-1 reverse transcriptase, utilized in blend with other antiretroviral agents for the treatment of HIV-1 infection.

Herbs used as bioavailability enhancers

Cuminum cyminum

Natural bio-enhancer *C. cyminum* commonly called cumin is found as a little and meager yearly spice, grown extensively in South-East Europe and North Africa circumscribing the Mediterranean Sea. It is a powerful gastric energizer, useful in stomach protuberance and flatulence. It has curatively been used as an anti-diarrheal agent, galactagogue, diuretic, and helpful in hoarseness of voice. Bioefficacy enhancing activity of cumin is revealed toward various medications. Different volatile oils and flavonoids have shown bioavailability improving activity. For the most, luteolin has proved to be a robust P-glycoprotein inhibitor in the writing [50-52].

Z. officinale

Ginger is the rhizome of *Z. officinale* belonging to family Zingiberaceae, powerfully affects GIT mucous film. It manages the functions of intestine to ease absorption. 10–30 mg/kg body weight range of ginger acts as a bio-enhancer. Example of various antibiotics whose bioavailability rose by it includes, azithromycin (85.0%), erythromycin (10.5%), cephalexin (85.0%), cefadroxil (65.0%), amoxicillin (90.0%), and cloxacillin (90.0%) are expanded by it [53].

Aloe vera

It is dried juice collected by incision, from the bases of the leaves of various species of aloe, *Aloe perryi*, *A. vera* or *Aloe barbadensis,* and *Aloe ferox*, belonging to family Liliaceae. There are two different preparation of *A. vera*, that is, entire leaf extract and gel-filled inside, which showed the increased absorption of both the Vitamins C and E. Various studies concluded, *A. vera* as an exceptionally promising future nutritional herbal bio-enhancer [54].

Turmeric

It is a spice used for centuries in Ayurveda for therapeutic purposes and also in Indian kitchens for adding color and flavor to the food. It is called as Haldi in Hindi. It is derived from dried as well as fresh rhizomes of the plant known as *Curcuma Longa*, belonging to family

Zingiberaceae. Turmeric contains a flavonoid called curcumin, which suppresses metabolizing enzymes like CYP3A4 in the liver. It is also capable of initiating an adjusting drug transporter P-gp; consequently increases the bioavailability of celiprolol and midazolam in rats. The bio-enhancing property of curcumin is analogous to piperine. Curcumin put down the UDP-glucuronyl transferase level in intestine and hepatic tissues. It likewise changes the physiological activity in the GIT promoting better absorption of drugs [55].

Bioenhancers of non-herbal origin

Capmul

Capmul MCM C10, which is a glyceryl monocaprate, is one of the greatly utilized bio-enhancers. Its production is from edible fats and oils which is commonly used in lip products. In a study did on rats of antibiotic ceftriaxone when co-administered with capmul, enhanced its bioavailability by 80% [17].

Cow urine distillate

It is more effective as bio-enhancer than cow urine. The potency of antimicrobial, antifungal, and anti-cancer drugs is enhanced by it. The US Patents (No. 6896907 and 6410059) has been granted to cow urine for its medicinal properties, especially as a bio-enhancer with antibiotics, antifungal, and anti-cancer drugs. The potency of paclitaxel, observed to increase against MCF-7, a human breast cancer cell line, in *in vitro* assays (US Patent No. 6410059) [56,57]. The cow urine distillate enhanced the rifampicin action by about 5–7 times against *Escherichia coli* and 3–11 times against Gram-positive bacteria. It most likely acts by improving the transport of antibiotics across the digestive tract membrane. The improvement in transport is roughly 2–7 folds. The gonadotropin-releasing hormone conjugate deleteriously affects the reproductive hormones and estrous cycle of female mice, and distillate of cow urine acts as a bio-enhancer in immunization efficacy adjust these impacts [58].

Need for bioavailability enhancers

Because of an expansion in the no. of medical advancement likewise, there is an increase in various side effects created by them. By the utilization of bio-enhancers, the dose can diminish to a great extent, which can assist to lessen the possibilities of side effects. Several plant extracts and phytoconstituents, even with incredible bioactivity *in vitro*, show less or no *in vivo* actions, because of their helpless lipid solubility or inappropriate atomic size or both, bringing about poor absorption, and poor bioavailability. It was found that when single constituents were confined from the plant extract, there is a loss of particular bio-activity. Sometimes certain parts of the multi-constituent plant extract are demolished in the gastric condition when taken orally. They lower the dose, abbreviate the treatment time frame, and accordingly diminish drug resistance issues. Because of the dose economy, they make treatment financially savvy; minimize drug toxicity, and unfavorable responses.

Problems/disadvantages/hurdles with bio-enhancers

As the bio-enhancers have a chemical entity in them, they can have their reactions as well, and when administered alongside other drugs, may end up in interactions and other side effects. However, a portion of the difficulties experienced have been solved by modifying the physicochemical characteristics of the nanomaterials to enhance properties such as high circulation within the blood, expanded functional surface area, and protection of the incorporated drug from degradation, the crossing of biological barriers, and site-specific targeting. Another test of innovative work in the development of herbal bio-enhancers is large scale production. There is consistently a requirement to scale up laboratory or pilot innovations for possible commercialization. Making the nano or microparticles and maintaining their size and also to convenience with the medications is likewise a significant issue [59].

Advances in natural bio-enhancers likewise give new difficulties to administrative control. There is an expanding need to have guidelines that would represent the physicochemical and pharmacokinetics of nano-drug products, which are not quite the same as traditional medication items. The United States' Food and Drug Administration and the European Medicines Evaluation Agency have taken the initiative to recognize some possible scientific and regulatory challenges [20].

Relation of bioenhancers with ayurveda

Present-day science is developing bio-enhancers as a new science for expanding the adequacy of medication, still this concept was started and was documented hundreds of years back and was utilized as a system of medicine. In Ayurveda, several herbs were used, such as *P. longum*, *Z. officinale*, and *G. glabra* having action as bio-enhancers and different strategies for bio-enhancing for centuries. There are various concepts and techniques in Ayurveda such as

- Yogavahi,
- Anupana,
- Bhaishajya Kala,
- Bhavana (trituration),
- Rasayana,
- Yoga (formulations), and
- Kalpanas (various dosage forms).

The different ideas of Purana Aushadhies (old drugs), the concept of activity increasing medications, and penetration enhancers had been used since ancient time in Ayurveda. Besides, Samshodhana (bio-purification) can be considered for this idea. The definite investigation of these ideas clarifies the idea of bio-enhancers [60].

Ideal property of bio-enhancers

The ideal bio-enhancers need to be [61-73]

- Nontoxic, non-allergenic, and non-irritating,
- Produce own pharmacological effects,
- Rapid-acting with predictable and reproducible activity,
- Unidirectional in action,
- Compatible with other active pharmaceutical ingredients,
- Stable with time and environment,
- Easily formulated into a various dosage form, and
- Easily available and cost-effective.

Recent advancement in bioenhancers

Various formulations made by the advancements in bio-enhancers are as follows

- Quercetin liposome: It is a formulation with biological activity as an anti-oxidant, anti-cancer with the active ingredient quercetin. It can be prepared by the reverse evaporation technique. It has the benefits of reducing the dose, enhancing penetration in the blood-brain barrier, given by the intranasal route [1].
- Liposome encapsulated silymarin: Silymarin is an active constituent that improves the bioavailability of formulation. It has hepatoprotective activity, given by the buccal route. Its preparation is also by reverse evaporation technique [64].
- Rutin-alginate chitosan microspheres: Its target is cerebrovascular system. The main component as rutin, it is given intravenously. Its formulation is by complex coacervation method [65].
- Zedoary oil microspheres: This formulation is hepatoprotective with the main ingredient as zedoary. The technique for its preparation is quasi emulsion solvent diffusion. It is a sustained release and is highly bioavailable with the oral route of administration [66].
- Triptolide nanoparticles: This formulation has anti-inflammatory activity with enhanced penetration of the drug through stratum corneum by hydration. The active ingredient is triptolide having a topical route of administration. The method of preparation is an emulsification ultrasound [67].
- Radix salvia miltiorrhiza nanoparticle: This formulation of radix salvia has biological activity in coronary heart disease, angina pectoris, and myocardial infarction tested *in vitro*. Preparation is through the spray drying technique [68].
- Capsaicin transferosomes: It is a topically applied formulation having analgesic activity. Capsaicin is its active ingredient with increased skin penetration [69].

- Colchicine transferosomes: This formulation tested *in vitro* for gout treatment having good skin penetration [70].
- Ginseng lipid-based system: It is a nutraceutical immune modulator having flavonoids as active constituent. It has oral route of administration and prepared by phospholipid complexation technique [71].
- Green tea lipid-based system: It is a nutraceutical with ginsenoside as the active ingredient, has antioxidant, and anti-cancer properties. Prepared by the phospholipid complexation technique [72].

Recent patents on herbal controlled release formulation [73]

Novel drug delivery system	Active ingredient	US patent no.
Nasal spray	Opioid analgesic and aloe	US 5948414
Microencapsulated and controlled release formulation	Ginsenoside	US 6340478 B1
Microencapsulated formulation	Isoflavones	US 6890561 B1
Transdermal delivery system	Alkaloids of aconitum species	US 6896898 B1
Brain tonic	Sesamum indicum oil and Centella asiatica alcoholic extract	US patent 2005 / 0142232 A
Herbal tablet dosage form	Glycine max containing 7s globulin protein extract, curcumin, Zingiber	US patent 2007 / 0042062 A1
Transdermal patch	Opioid analgesic (phenanthrene)	US patent 2007 / 0077284 A1
Microgranules	Flavonoids and terpenes	US patent 7569236132

Employment of silver and gold nanoparticles by the use of plant extracts

There are many pharmaceutical uses of nanoparticles. When the silver nitrate solution is contacted with geranium (*Pelargonium graveolens*) leaf extract, a rapid reduction of the silver ions was observed [74]. The preparation used to reduce Ag+ ions to Ag is an extract produced by taking 20 g of chopped and washed geranium leaves with 100 mL of distilled water in a 500 mL Erlenmeyer flask. The suspension was boiling for 1 min. A volume of 5 mL of pure broth added to 100 mL of 0.001 mol/L aqueous solution of AgNO3. The ultraviolet (UV)-visible spectrum helps to estimate the bioreduction of the Ag+ ions of the solution.

With neem leaf extract, a competitive reduction of Au3+ and Ag+ ions co-occur in solution. It has led to the synthesis of bimetallic Au core- Ag shell nanoparticles in solution [75]. Using the new sundried biomass of *Cinnamomum camphora* leaf silver nanoparticles ranging from 55 to 80 nm inside and triangular or spherical gold nanoparticles were fabricated. The preparation of gold nano triangles by leaf of camphor tree is done at ambient temperature firmly relied on the measure of dried biomass. This biomass offered adequate defensive biomolecules [76].

A process of applying A. vera leaf extract used for making gold nano triangles and spherical silver nanoparticles could be utilized. The kinetics is estimated by UV-visible absorption spectroscopy and transmission electron microscopy [70].

Other recent advances

- Ketoprofen-loaded solid lipid nanoparticles (SLNs) made from beeswax and carnauba wax was evaluated by Kheradmandnia *et al.* They discovered that the average particle size of medication loaded SLNs decline on blending with Tween 80 and egg lecithin also on expanding total concentration of surfactant. The ability of SLNs to incorporate a poorly water-soluble drug such as ketoprofen, revealed by high drug entrapment efficiency (EE) of 97% [77].
- Curcuminoids- loaded SLNs are formulated and characterized by Tiyaboonchai *et al*. They noticed that lyophilized curcuminoids loaded SLNs showed bio-enhancement of up to 70% (w/w) with spherical particles of mean particle size 450 nm and 0.4 as polydispersity index [78].
- Emodin-loaded SLNs (E-SLNs) preparation evaluation; characterization; and antitumor activity were studied by Wang and group. The investigation of physicochemical properties of the E-SLNs was by particle size analysis, zeta potential measurement, drug EE, stability, and *in vitro* drug release behavior. The medication liberated by E-SLNs last for 72 h and displayed a sustained profile, which made it a favorable oral drug delivery system [79].
- SLNs-coated Silk fibroin was also developed by an emulsification and solidification method using sodium lauryl sulfate (an anionic surfactant) as a stabilizer. Then, the SLN was covered with silk fibroin under an acidic condition by electrostatic interaction. The silk fibroin layer of nanoparticles contains positive charge; hence, it shows good interaction with oppositely charged skin cells, improving the permeability of skin [80].
- The cellular uptake of SLNs and cytotoxicity of encapsulated paclitaxel in A549 cancer cells were investigated by Yuan *et al*. The modified SLN with PEG and folate could upgrade the SLN cellular uptake and the cellular cytotoxicity of the medication that improves folate receptor mediated endocytosis [81].
- SLNs as the topical carrier for epidermal targeting of podophyllotoxin (P-SLN) were evaluated by Chen *et al*. [82].
- The potential use of SLNs in dermatology and cosmetics, incorporated in a hydrogel or o/w-cream was tested and its influence on drug penetration into porcine skin was given by Jenning and group [83].
- Piperine was found in both long pepper and black pepper as the potent bio-enhancer was studied by Singh *et al*. Piperines can improve the binding ability of rifampicin to RNA polymerase [84].
- Nanotechnology-based combination drug delivery to tumor tissues was reported by Parhi *et al*. It emerged as an effective for delivery of anticancer drugs [85].
- Rajendran *et al*. prepared the ethanolic extract of Ocimum sanctum, which was loaded inside the sodium alginate chitosan nanoparticles by cation induced controlled gellification method and finished on cotton fabric by pad dry cure method. This examination uncovered that the herb encapsulated nanoparticle could act as a biocontrol agent against microscopic organisms in fabrics [86].

Future prospects

Using the bio-enhancers, the dose requirement can be diminished, and the dangers of drug resistance and other side effects can be minimized. Many drugs are very useful but have great side effects and toxicity (chemotherapy drugs, e.g., taxol) by the use of bio-enhancers; their toxicity chances can reduce. As the dosage is reduced, prescription needed is less; hence, it is economically beneficial too. Hence, use of bio-enhancers in modern medicine can give rise to the development of safer, better, and effective medicine.

CONCLUSION

Bio-enhancer, which is a new and innovative concept, was well stated in Ayurveda and used for ages. The use of compounds derived from nature, having very less or no therapeutic activity but can help in improving the action of the active ingredient used along with them can be a very good step in medical field. The combination of new medical science technique and the concept of natural bio-enhancers, can lead to a perfect novel drug delivery system that can reduce drug cost by decreasing the required dose, reduced toxicity, lessen the side effects, and can provide various other advantages. This combined concept if will be used in our country having good knowledge of Ayurveda can lead to increased economy of the state, good position in the medical science concerning other countries and will be a better life-saving concept which can be easily made available for every section of society at a reasonable cost.

CONFLICTS OF INTEREST

None.

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None.

AUTHORS CONTRIBUTION

All authors have contributed equally.

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