



Contents lists available at ScienceDirect

## Asian Pacific Journal of Tropical Biomedicine

journal homepage: [www.elsevier.com/locate/apjtb](http://www.elsevier.com/locate/apjtb)

Document heading doi:10.1016/S2221-1691(13)60060-X © 2013 by the Asian Pacific Journal of Tropical Biomedicine. All rights reserved.

## Bioavailability enhancers of herbal origin: An overview

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## PEER REVIEW

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## Comments

Exhaustive analysis of the literature available has been carried out by the authors and their team. Almost all the publications based on the topic had been covered. The researchers are now aimed at methods of increasing the bioavailability of various plant extract which has been available to a wider section of the society. Hence, it has been proved that novel drug delivery system of herbal as well as of chemical origin has been used to increase the bioavailability of the compounds or their respective constituents (as in case of herbal extracts).  
 (Details on Page 263)

## ABSTRACT

Recently, the use of herbal medicines has been increased all over the world due to their therapeutic effects and fewer adverse effects as compared to the modern medicines. However, many herbal drugs and herbal extracts despite of their impressive *in-vitro* findings demonstrates less or negligible *in-vivo* activity due to their poor lipid solubility or improper molecular size, resulting in poor absorption and hence poor bioavailability. Nowadays with the advancement in the technology, novel drug delivery systems open the door towards the development of enhancing bioavailability of herbal drug delivery systems. For last one decade many novel carriers such as liposomes, microspheres, nanoparticles, transferosomes, ethosomes, lipid based systems *etc.* have been reported for successful modified delivery of various herbal drugs. Many herbal compounds including quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin and nitrile glycoside have demonstrated capability to enhance the bioavailability. The objective of this review is to summarize various available novel drug delivery technologies which have been developed for delivery of drugs (herbal), and to achieve better therapeutic response. An attempt has also been made to compile a profile on bioavailability enhancers of herbal origin with the mechanism of action (wherever reported) and studies on improvement in drug bioavailability, exhibited particularly by natural compounds.

## KEYWORDS

Bioavailability, Herbal, Novel Drug Delivery System, Nanotechnology, Bioenhancer, Formulation

## 1. Introduction

Herbal medicine is a practice as old as mankind and during the last century chemical and pharmacological studies have been performed on a lot of plant extracts in order to know their chemical composition and to confirm the indications of traditional medicine<sup>[1]</sup>. Ayurveda has made a major contribution to the drug discovery process through reverse pharmacology, with new means of identifying active compounds and reduction of drug development costs<sup>[2]</sup>. Recent developments of another Ayurveda-based technology, this time, enhancing bioavailability of drugs, have produced

a revolutionary shift in the way medicines are administered. Phytochemical and phytopharmacological studies have long been established overall health boosting capacities of various plant products but there is a great interest and medical need for the improvement of bioavailability of a large number of herbal drug and plant extract which are poorly lipid soluble and so are less bioavailable<sup>[3]</sup>.

Many herbal drugs and herbal extracts despite of their extraordinary potential *in-vitro* finding, demonstrate less or no *in-vivo* actions due to their poor lipid solubility or improper molecular size or both, ultimately resulting in poor absorption and poor bioavailability.

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Foundation Project: Supported by AICTE – MODROBS Grant (Grant No. 8024/RID/BOR/MOD-

458/2009–10).

Article history:

Received 10 Jan 2013

Received in revised form 25 Jan, 2nd revised form 11 Feb, 3rd revised form 25 Feb 2013

Accepted 7 Mar 2013

Available online 28 Apr 2013

Various components of an extract may contribute to the synergistic action of the extract and treatment like purification and separation can lead to a partial loss of specific activity due to the removal of chemically related substances contributing to the activity of the main components. Very often the chemical complexity of the extract seems to be important for the bioavailability of the active components.

Most of the plant constituents, specifically phenolics, are water soluble and so the major problem for less bioavailability is the inability to cross the lipid membranes of intestine. The bioavailability can be improved with the use of different novel delivery systems like liposomes, marinosomes, niosomes and lipid based systems which can enhance the rate of release as well as the capacity to cross the lipid rich biomembranes<sup>[4]</sup>.

Phospholipids based drug delivery systems have been found to be promising for the effective and efficacious herbal drug delivery. The effectiveness of any herbal product (or medication) is dependent upon delivering an effective level of the active compounds<sup>[5]</sup>.

## 2. Concept of bioavailability enhancers

The concept of 'bioavailability enhancers' is derived from the traditional age old system of Ayurveda (science of life). In Ayurveda, black pepper, long pepper and ginger are collectively known as "*Trikatu*". In Sanskrit "*Trikatu*" means three acrids.

The action of bioenhancers was first documented by Bose (1929) who described the action of long pepper to *Adhatoda vasika* leaves increased the antiasthmatic properties of *Adhatoda vasika* leaves.

## 3. Definition and history of bioavailability enhancers

'Bioavailability enhancers' are drug facilitators, they are the molecules which by themselves do not show typical drug activity but when used in combination they enhance the activity of drug molecule in several ways including increasing bioavailability of the drug across the membrane, potentiating the drug molecule by conformational interaction, acting as receptors for drug molecule and making target cells more receptive to drugs. A 'bioenhancer' is an agent capable of enhancing bioavailability and bioefficacy of a particular drug with which it is combined, without any typical pharmacological activity of its own at the dose used.

These are also termed as 'absorption enhancers' which are functional excipients included in formulations to improve the absorption of a pharmacologically active drug.

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, Jammu), who discovered and scientifically validated piperine as the world's first bioavailability enhancer in 1979<sup>[6]</sup>.

C.K. Atal, the Director of the institute 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* (*P. longum*) (210 formulations out of 370 reviewed) which is used in a large variety of diseases. He formed the working hypothesis that *Trikatu* increased the efficacy of formulations. *Trikatu* has three ingredients: black pepper

(*Piper nigrum*), long pepper (*P. longum*) and ginger (*Zingiber officinale*). Based on this hypothesis, these ingredients were studied, which found that one of the ingredients, '*P. longum*', '*Piper*' increased the bioavailability of many drugs<sup>[7]</sup>.

Piperine, the active principal present in *P. longum* was isolated and its bioavailability enhancing action was established. Further research on several classes of drugs including antitubercular, leprosy, antibiotics, non-steroidal antiinflammatory drugs, 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<sup>[8]</sup>.

However it was also noted that piperine did not increase bioavailability of all drugs, while with some drugs the effect was found to be inconsistent.

## 4. Drug absorption barriers

The drug must cross the epithelial barrier of the intestinal mucosa for it to be transported from the lumen of the gut into the systemic circulation and exert its biological actions. There are many anatomical and biological barriers for the oral drug delivery system to penetrate the epithelial membrane<sup>[9]</sup>.

There are many structures in the intestinal epithelium which serve as barriers to the transfer of drugs from the gastrointestinal track to the systemic circulation. An aqueous stagnant layer due its hydrophilic nature is potential barrier to the absorption of drugs<sup>[10]</sup>.

The drug molecules larger than about 0.4 nm have difficulty in passing through these aqueous channels<sup>[10]</sup>.

Recent work has shown that drug efflux pumps like P-glycoprotein possess a very important role in inhibiting efficient drug entry into the systemic circulation<sup>[11]</sup>.

P-glycoprotein is a type of ATPase and an energy dependent transmembrane drug efflux pump, it belongs to members of ABC transporters. It has a molecular weight of ~170 kDa and has 1280 amino acid residues<sup>[12]</sup>.

## 5. Methods for enhancement of bioavailability of orally administered drug

### 5.1. Absorption enhancers

Many of the absorption enhancers are effective in improving the intestinal absorption, such as bile salts, surfactants, fatty acids, chelating agents, salicylates and polymers<sup>[13,14]</sup>. Chitosan, particularly trimethylated chitosan, increases the drug absorption via paracellular route by redistribution of the cytoskeletal F-actin, causing the opening of the tight junctions. Bile, bile salts and fatty acids are surfactants which act as absorption enhancers by increasing the solubility of hydrophobic drugs in the aqueous layer or by increasing the fluidity of the apical and basolateral membranes. Calcium chelators such as ethylene glycol tetraacetic acid and ethylene diamine tetraacetic acid (EDTA) enhance absorption by reducing the extracellular calcium concentration, leading to the disruption of cell-cell contacts<sup>[15]</sup>.

### 5.2. Prodrugs

Various ampicillin derivatives are one of the well-known examples of increasing the lipophilicity of agents to enhance absorption of a polar drug by prodrug strategy<sup>[16]</sup>.

Ampicillin due to its hydrophilic nature is only 30%–40% absorbed from the gastrointestinal tract (GIT). By esterification of carboxyl group of ampicillin the prodrugs of ampicillin such as pivampicilline, bacampicillin and talampicillin were synthesized.

### 5.3. Dosage form and other pharmaceutical approaches

Various dosage formulations such as liposomes and emulsions enhanced the intestinal absorption of insoluble drugs<sup>[17,18]</sup>. Particle size reduction such as micronization, nanoparticulate carriers, complexation and liquid crystalline phases also maximize drug absorption<sup>[19,20]</sup>.

### 5.4. P-glycoprotein inhibitors

P-glycoprotein inhibitors reverse P-glycoprotein-mediated efflux in an attempt to improve the efficiency of drug transport across the epithelial membrane. P-glycoprotein inhibitors influence metabolism, absorption, distribution, and elimination of P-glycoprotein substrates in the process of modulating pharmacokinetics<sup>[21]</sup>.

## 6. Mechanism of action of bioenhancers of herbal origin

There are several mechanisms of action by which herbal bioenhancers act. Different herbal bioenhancers may have same or different mechanisms of action. Nutritional bioenhancers enhance absorption by acting on gastrointestinal tract. Antimicrobial bioenhancers mostly act on drug metabolism processes.

Among the various mechanisms of action postulated for herbal bioenhancers some are (a) reduction in hydrochloric acid secretion and increase in gastrointestinal blood supply<sup>[22]</sup>, (b) inhibition of gastrointestinal transit, gastric emptying time and intestinal motility<sup>[23,24]</sup>, (c) modifications in GIT epithelial cell membrane permeability<sup>[25,26]</sup>, (d) cholagogous effect<sup>[25]</sup>, (e) bioenergetics and thermogenic properties<sup>[25,27]</sup> and (f) suppression of first pass metabolism and inhibition of drug metabolizing enzymes<sup>[27]</sup> and stimulation of gamma glutamyl transpeptidase (GGT) activity which enhances uptake of amino acids<sup>[28]</sup>.

### 6.1. Mechanism of action of piperine

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<sup>[29]</sup>.

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.

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 and UDP-glucuronyltransferase activities<sup>[30]</sup>.

Another study demonstrates that piperine modifies the rate of glucuronidation by lowering the endogenous UDP-glucuronic acid content and also by inhibiting the transferase

activity<sup>[31]</sup>.

Piperine inhibits human P-glycoprotein and cytochrome P450 3A4 (CYP3A4)<sup>[32]</sup>. Both the proteins contribute to a major extent to first-pass elimination of many drugs.

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<sup>[33]</sup>.

## 7. Need for bioavailability enhancers

Lipid solubility and molecular size are the major limiting factors for molecules to pass the biological membrane and to be absorbed systematically following oral or topical administration.

Several plant extracts and phytoconstituents, despite having excellent bioactivity *in vitro* demonstrate less or no *in vivo* actions due to their poor lipid solubility or improper molecular size or both, resulting poor absorption and poor bioavailability. It is often found that, when individual constituents are isolated from the plant extract there is loss of specific bio-activity. Sometimes some constituents of the multi-constituent plant extract are destroyed in gastric environment when taken orally. They reduce the dose, shorten the treatment period and thus reduce drug resistance problems. Due to dose economy, they make treatment cost-effective, minimize drug toxicity and adverse reactions.

## 8. Problems/disadvantages/hurdles with bioenhancers

Although bio-enhancers in drug delivery has been successful, not all approaches have met with the same success. New bio-enhancers being developed come with challenges which have to be solved. However some of the challenges encountered have been and are still being tackled by modifying the physicochemical characteristics of the nanomaterials to improve properties such as long circulation in the blood, increased functional surface area, protection of incorporated drug from degradation, crossing of biological barriers and site-specific targeting.

Another challenge of research and development of herbal bio-enhancers is large scale production. There is always a need to scale up laboratory or pilot technologies for eventual commercialization. The challenges of scaling up include low concentration of nanomaterials, agglomeration and the chemistry process—it is easier to modify nanomaterials at laboratory scale for improved performance than at large scale<sup>[34]</sup>. Maintaining the size and composition of nanomaterials that enhances bioavailability at large scale is also a challenge.

Advances in herbal bio-enhancers also provide new challenges for regulatory control. There is an increasing need to have regulations that would account for physicochemical and pharmacokinetic properties of nano drug products, which are different from conventional drug products. The United States' Food and Drug Administration and the European

Medicines Evaluation Agency have taken the initiative to identify some possible scientific and regulatory challenges[34].

## 9. Future prospects

With bioenhancers the dosage is reduced and dangers of drug resistance are minimized. Toxicity of drug is minimized because of reduced dosage; This is especially true of anticancer drugs like taxol.

There are ecological benefits too. Taxol used to treat ovarian cancer or breast cancer is derived from bark of pacific yew tree, one of the slowest growing tree in the world. At present to treat one patient, six trees of 25–100 years old needed to be axed. With bioenhancers fewer will be destroyed.

## 10. Role of natural compounds from medicinal plants as drug bioavailability enhancers

### 10.1. Quercetin

(2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4Hchromen-4-one) is a flavonoid, an aglycone form of a number of other flavonoid glycosides found in citrus fruits.

Quercetin has exhibited a wide range of beneficial biological activities including antioxidant, radical scavenging, anti-inflammatory, anti-atherosclerotic, anti-tumoral and anti-viral effects[35]. Quercetin has been shown to increase bioavailability, blood levels and efficacy of a number of drugs including diltiazem, digoxin and epigallocatechin gallate[36–39].

The plasma concentrations, the area under the plasma concentration–time curve (AUC) and peak concentration [C(max)] of diltiazem in the rabbits pretreated with quercetin were significantly higher than those obtained from untreated group. It was reported that diltiazem is metabolized by CYP3A4 both in the liver and small intestine[40,41]. The absorption of diltiazem in the intestinal mucosa was inhibited by P-glycoprotein efflux pump[42,43]. The increased AUCs and C(max) of diltiazem by pretreatment of quercetin might have been resulted from the inhibition of the P-glycoprotein efflux pump and the metabolizing enzyme, CYP3A4 in the intestinal mucosa[44,45] and restraint of the metabolizing enzyme, CYP3A4[46].

The absorption of epigallocatechin gallate was also reported to be enhanced with red onion supplementation, abundant source of quercetin. The AUC of epigallocatechin gallate determined over a period of 6 h increased from 1323 to 1814 ng/h/mL, when co-administered with quercetin. It was demonstrated that increased amount of quercetin administered along with epigallocatechin gallate could increase absorption of epigallocatechin gallate from the intestine[39].

### 10.2. Genistein

Genistein (5,7-Dihydroxy-3-(4-hydroxyphenyl)chromen-4-one) belongs to the isoflavone class of flavonoids. It is also well known as a phytoestrogen[47]. Since genistein was reported to be able to inhibit P-glycoprotein, BCRP and MRP2 efflux function, the intestinal absorption of paclitaxel, a substrate for efflux transports such as P-glycoprotein, BCRP and MRP2 was dramatically increased[48–50], co-administered with genistein.

The inhibition of the efflux transporters by genistein

also contributed the improvement of systemic exposure of paclitaxel[51]. The presence of genistein (10 mg/kg) caused an increase in AUC (54.7%) and a decrease in the total plasma clearance (35.2%) after oral administration of paclitaxel at a dose of 30 mg/kg in rats.

### 10.3. Naringin

Naringin is the major flavonoid glycoside found in grapefruit and makes grapefruit juice taste bitter. Naringin exerts a variety of pharmacological effects such as antioxidant, blood lipid lowering and anticarcinogenic activities. Also, naringin was reported to inhibit and CYP3A1/2 and P-glycoprotein in rats[52,53]. Oral naringin (3.3 and 10.0 mg/kg) was pretreated 30 min before intravenous administration of paclitaxel (3 mg/kg) and after intravenous administration of paclitaxel, the AUC was significantly improved (40.8% and 49.1% for naringin doses of 3.3 and 10 mg/kg, respectively)[53].

### 10.4. Sinomenine

Sinomenine (7,8-didehydro-4-hydroxy-3,7-dimethoxy-17-methylmorphan-6-one) is an alkaloid extracted from *Sinomenium acutum* Thunb[54]. Paeoniflorin is a bioactive monoterpene glucoside, which has been widely used to treat inflammation and arthritic conditions. Paeoniflorin has a poor absorption rate and thus a very low bioavailability (3–4%) when administered orally[55]. Co-administration with sinomenine dramatically altered the pharmacokinetic behaviors of paeoniflorin in rats[56].

The results of AUC obtained in the study, demonstrated that oral bioavailability of paeoniflorin was enhanced by more than 12 times in rats treated with sinomenine. The mechanism underlying this improvement of bioavailability of paeoniflorin may be explained by, that sinomenine could decrease the efflux transport of paeoniflorin by P-glycoprotein in the small intestine[57].

### 10.5. Glycyrrhizin

Glycyrrhizin [(3,18)-30-hydroxy-11,30-dioxoolean-12-en-3-yl 2-O-glucopyranuronosyl-Dglucopyranosiduronic acid] is a triterpenoid saponin found in *Glycyrrhiza glabra* L. (Fabaceae). Glycyrrhizin showed a more potent absorption enhancing activity than caproic acid at the same concentration tested[58]. 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[59]. The absorption enhancing activity of glycyrrhizin was increased by presence of the other absorption enhancers[58].

### 10.6. Nitrile glycosides

Nitrile glycosides and its derivatives are components derived from the pods of *Moringa oleifera* L. They do not possess drug activity of their own but are reported to promote and augment the biological activity, bioavailability or the uptake of drugs in combination therapy. The nitrile glycoside (e.g. niaziridin) has enhanced the absorption of commonly used antibiotics such as rifampicin, tetracycline and ampicillin, vitamins and nutrients[60].

In bioactivity test, niaziridin-rich fraction of *Moringa oleifera* remarkably enhanced activity of rifampicin, ampicillin and nalidixic acid by 1.2–19 folds against both

the Gram positive and negative strains by enhancing drug absorption in culture model<sup>[60]</sup>.

### 10.7. *Cuminum cyminum* Linn.

*Cuminum cyminum* Linn. is a small and thin annual herb, grown extensively in South–East Europe and North Africa bordering the Mediterranean sea. It is an effective gastric stimulant, beneficial in abdominal lump and flatulence. It has therapeutically been used as an anti–diarrheal, galactagogue, diuretic and also beneficial in hoarseness of voice<sup>[61]</sup>. Bioavailability/bioefficacy enhancing activity of *Cuminum cyminum* L. was revealed toward a number of drugs<sup>[62]</sup>. Various volatile oils and luteolin and other flavonoids were seemed to attribute the bioavailability/bioefficacy enhancing activity. Especially, luteolin has demonstrated to be a potent P–glycoprotein inhibitor in the literature<sup>[63]</sup>.

### 10.8. *Zingiber officinale* (*Z. officinale*)

Ginger (*Z. officinale*) has a powerful effect on GIT mucous membrane. It regulates the intestinal function to facilitate absorption. Ginger is used in the range of 10–30 mg/kg body weight as bioenhancer. The bioavailability of different antibiotics like azithromycin (85.0%), erythromycin (10.5%), cephalexin (85.0%), cefadroxil (65.0%), amoxicillin (90.0%) and cloxacillin (90.0%) are increased by it<sup>[64]</sup>.

### 10.9. *Lysergol*

Lysergol, a phytomolecule, is isolated from higher plants like *Rivea corymbosa*, *Ipomoea violacea* and *Ipomoea muricata*. It enhances the killing activities of different antibiotics on bacteria and is a promising herbal bioenhancer<sup>[65]</sup>.

### 10.10. *Allium sativum*

Allicin, the active bioenhancer phytomolecule in garlic enhances the fungicidal activity of amphotericin B against pathogenic fungi such as *Candida albicans*, *Aspergillus fumigatus* and yeast *Saccharomyces cerevisiae*. Amphotericin B when given along with allicin exhibited enhanced antifungal activity against the common yeast known as *Saccharomyces cerevisiae*<sup>[66]</sup>.

### 10.11. *Aloe vera* (*A. vera*)

The results of two different *A. vera* preparations, *i.e.*, whole leaf extract and inner filled gel indicate that the aloe improve the absorption of both the vitamin C and E. The absorption is slower and vitamins last longer in the plasma with aloe, this increases bioavailability of vitamin C and E in human<sup>[67]</sup>. *A. vera* is a very promising future nutritional herbal bioenhancer.

## 11. Various lipid technologies for enhancing bioavailability

The available lipids for enhancing bioavailability are liposomes, microspheres, nanoparticles, transferosomes, ethosomes, nanoemulsions/microemulsions, lipid based systems, polymeric micelle formulation and other novel vesicular herbal formulation. Many researchers have worked on bioavailability enhancers of herbal origin from time to

time. Some of their works are enlisted in Table 1–7.

## 12. Biosynthesis and application of silver and gold nanoparticles using plant extract

An important branch of biosynthesis of nanoparticles is the application of plant extract to the biosynthesis reaction.

A rapid reduction of the silver ions was observed when the silver nitrate solution was contacted with geranium (*Pelargonium graveolens*) leaf extract<sup>[87]</sup>.

The extract used for reduction of Ag<sup>+</sup> ions to Ag was prepared by taking 20 g of thoroughly washed and finely cut geranium leaves in a 500 mL Erlenmeyer flask with 100 mL of distilled water. The suspension was boiling for 1 min. A volume of 5 mL of pure broth was added to 100 mL of 0.001 mol/L aqueous solution of AgNO<sub>3</sub>. The bioreduction of the Ag<sup>+</sup> ions was monitored by measuring the UV–vis spectra of solution.

In the case of neem leaf extract a competition reduction of Au<sup>3+</sup> and Ag<sup>+</sup> ions presented simultaneously in solution was observed. It has led to the synthesis of bimetallic Au core–Ag shell nanoparticles in solution<sup>[87]</sup>.

Silver nanoparticles ranging from 55 to 80 nm in size and triangular or spherical gold nanoparticles were fabricated using the novel sundried biomass of *Cinnamomum camphora* leaf<sup>[88]</sup>. It was found that formation of gold nanotriangles by *Cinnamomum camphora* leaf at ambient temperature strongly depended on the amount of dried biomass. This biomass offered sufficient protective biomolecules.

A simple procedure applying *A. vera* leaf extract has been used for gold nanotriangle and spherical silver nanoparticles synthesis<sup>[89]</sup>. The kinetics of gold nanoparticles formation was monitored by UV–vis absorption spectroscopy and transmission electron microscopy (TEM). The effect of the amount of leaf extract on the synthesis of gold nanotriangles was investigated by observation of product formed.

Addition of *A. vera* extract to 0.001 mol/L aqueous solution of HAuCl<sub>4</sub> led to the appearance of a red color in solution after about 5 h of reaction. An analysis of the percentage of triangles formed in the reaction medium as a function of varying amounts of the *A. vera* extract showed that more spherical particles were formed with increasing amount of added extract.

*Eclipta alba* (known as Bhringraj) belongs to the family Asteraceae is rich in flavonoids, belonging to the group of phenolic compounds. The sample of 5 g of freshly collected leaves of *Eclipta* was washed for 10 min. and rinsed briefly in distilled water. Prepared biomaterial was taken in 250 mL capacity beaker having 200 mL of 50% Et–OH and was placed on boiling steam bath for 15 to 20 min.

## 13. Recent advances of bioenhancers

Kheradmandnia *et al.* evaluated the preparation and characterization of ketoprofen–loaded solid lipid nanoparticles (SLNs) made from beeswax and carnauba wax and found that the the mean particle size of drug loaded SLNs decreased upon mixing with Tween 80 and egg lecithin as well as upon increasing total surfactant concentration. High drug entrapment efficiency of 97% revealed the ability of SLNs to incorporate a poorly water–soluble drug such as ketoprofen. Differential scanning calorimetry thermograms and high–performance liquid chromatographic analysis indicated the stability of nanoparticles with negligible

**Table 1**  
Herbal liposomal formulations.

Formulation	Active ingredient	Application	Biological activity	Method of preparation	Percent entrapment efficiency	Route of administration	Ref.
Quercetin Liposome	Quercetin	Reduced dose, enhanced penetration in blood brain barrier	Anti-oxidant Anti-cancer	Reverse evaporation technique	60%	Intranasal	68
Liposome encapsulated Silymarin	Silymarin	Improve bioavailability	Hepato-protective	Reverse evaporation technique	69.22±0.6%	Buccal	69
Liposome <i>Artemisia arborescens</i>	Artemisiaarborescens	Targetting of essential oils to cells,enhance penetration into cytoplasmic barrier,	Antiviral	Film method and sonication	60–74%	<i>In-vitro</i>	70
Ampelopsin Liposome	Ampe-lopsin	increase efficiency	Anti-cancer	Film ultrasound method	62.30%	<i>In-vitro</i>	71
Paclitaxel Liposome	Paclitaxel	High entrapment efficiency and Ph sensitive	Anti-cancer	Thin film hydration method	94%	<i>In-vitro</i>	72
Curcumin Liposome	Curcumin	Long circulation with high entrapment efficiency	Anti-cancer	Ethanol injection method	88.27±2.16%	<i>In-vitro</i>	73
Garlicin Liposome	Garlicin	increase efficiency	Lungs	Reverse phase evaporation	90.77%	<i>In-vitro</i>	74

**Table 2**  
Microspheres.

Formulation	Active ingredient	Application	Biological activity	Method of preparation	Size in µm	Route of administration	Ref.
Rutin-alginate chitosan microspheres	Rutin	Targetting into cardiovascular and cerebrovascular system	Cardio-vascular and cerebro-vascular	Complex coecervation method	165–195	<i>In-vitro</i>	75
Zedoary oil microspheres	Zedoary	Sustained release and higher bioavailability	Hepato-protective	Quasi emulsion solvent diffusion method	100–600	Oral	76
CPT loaded microspheres	Campto-thecin	Prolonged release of camptothecin	Anti-cancer	Oil in water evaporation method	10	Intraperitoneal or intravenously	77
Quercetin microspheres	Quercetin	Significantly decreases the dose size	Anti-cancer	Solvent evaporation	6	<i>In-vitro</i>	78
<i>Cynara scolymus</i> microspheres	Cynara scolymus	Controlled release of nutraceuticals	Nutritional supplement	Spray drying technique	6–7	Oral	79

**Table 3**  
Nanoparticles.

Formulation	Active ingredient	Application	Biological activity	Method of preparation	% entrapment efficiency	Route of administration	Ref.
Triptolide nanoparticles	Triptolide	Enhance the penetration of drug through stratum corneum by increased hydration	Anti-inflam-matory	Emulsi-fication ultrasound		Topical	80
Nanoparticle of <i>Cuscuta chinensis</i>	Flavonoids and Lignans	Improve water solubility	Hepato-protective and anti-oxidant activity	Nano-suspension method	90%	Oral	81
Artemisinin nanocapsules	Arte-misinin	Sustained drug release	Anti-cancer	Self assembly procedure	90–93%	<i>In-vitro</i>	82
<i>Radix salvia miltiorrhiza</i> nanoparticles	<i>Radix salvia</i>	Improve the bio-availability	Coronary heart diseases, angina pectoris and myocardial infraction	Spray drying technique	96.68%	<i>In-vitro</i>	83
Taxol loaded nanoparticles	Taxol	Improve the bioavailability and sustained drug release	Anti-cancer	Emulsion solvent evaporation method	99.44%	<i>In-vitro</i>	84
Berberine loaded nanoparticles	Berberine	Sustained drug release	Anti-cancer	Ionic gelation method	65.40%	<i>In-vitro</i>	85
Naringenin loaded nanoparticles	Naringenin	Improve the release of NAR and improv its solubility	Hepato-protective	Nano-precipitation method		Oral	86

**Table 4**

Transferosomes.

Formulation	Active ingredient	Application	Biological activity	Droplet size	Route of administration	Ref.
Capsaicin transferosomes	Capsaicin	Increase skin penetration	Analgesic	150.6 nm	Topical	90
Colchicine transferosomes	Colchicine	Increase skin penetration	Antigout	–	<i>In-vitro</i>	91
Vincristine transferosomes	Vincristine	Increase entrapment efficiency and skin penetration	Anticancer	120 nm	<i>In-vitro</i>	92

**Table 5**

Lipid based herbal formulations.

Formulation	Active ingredient	Application	Biological activity	Method of preparation	Dose	Route of administration	Ref.
Ginkgo biloba lipid based systems	Flavonoids	Stabilizes ROS	Cardio-protective antioxidant activity	Phospholipid complexation	100 mg	Subcutaneous	93
Silybin lipid based systems	Flavonoids	Inhibits lipid peroxidation(LP) and stabilizes ROS	Hepatoprotective antioxidant	Phospholipid complexation	120 mg	Oral	94
Ginseng lipid based systems	Flavonoids	Increases absorption	Nutra-ceutical immune-modulator	Phospholipid complexation	150 mg	Oral	95
Greentea lipid based systems	Ginsenoside	Increases absorption	Nutra-ceutical, systemic antioxidant and anticancer	Phospholipid complexation	50–100 mg	Oral	95
Grapeseed lipid based systems	Epigallo-catechin	Increases absorption	systemic antioxidant	Phospholipid complexation	50–100 mg	Oral	95
Hawthorn lipid based systems	Procynidins	The blood TRAPn significantly elevated	Cardio-protective and anti-hypertensive	Phospholipid complexation	100 mg	Oral	96
Quercetin lipid based systems	Flavonoids	Exerted better therapeutic efficacy	Anti-oxidant and anticancer	Quercetin Phospholipid complexation		Oral	97
Curcumin lipid based systems	Curcumin	Increases antioxidant activity and increases bioavailability	Antioxidant and anticancer	Curcumin Phospholipid complexation	360 mg/kg	Oral	98

**Table 6**

Other novel vesicular herbal formulations.

Formulation	Active ingredient	Application	Biological activity	Droplet size	Route of administration	Ref.
Capsaicin transferosomes	Capsaicin	Increases skin penetration	Analgesic	150±6 nm	Topical	90
Colchicine transferosomes	Colchicine	Increases skin penetration		120 nm	<i>In-vitro</i>	91
Vincristine transferosomes	Vincristine	Increases entrapment efficiency and skin penetration	Anticancer	110±8 nm	<i>In-vitro</i>	92
Matrine ethosomes	Matrine	Improves subcutaneous permeation	Anti-inflammatory	350 nm	Topical	99
Ammonium glycyrrhizinate ethosomes	Ammonium glycyrrhizinate	Increase of invitro subcutaneous permeation	Anti Inflammatory	100 nm	Topical	100

**Table 7**

Recent patents on herbal controlled release formulations.

US patent No.	Active ingredients	Novel system incorporate	Ref.
US 5948414	Opioid analgesic and aloe	Nasal spray	101
US 6340478 B1	Ginsenosides	Microencapsulated and controlled release formulations	101
US6890561 B1	Isoflavones	Microencapsulated formulation	101
US6896898 B1	Alkaloids of aconitum species	Transdermal delivery system	101
US patent 2005/0142232 A	Oleaginous oil of <i>Sesamum indicum</i> and alcoholic extract of <i>Centella asiatica</i>	Brain tonic	101
US patent 2007/0042062 A1	Glycine max containing 7s globulin protein extract, curcumin, <i>Zingiber officinalis</i>	Herbal tablet dosage form	101
US patent 2007/0077284A1	Opioid analgesic (phenanthrene gp)	Transdermal patch	101
US patent 7569236132	Flavonoids (such as quercetin) and terpenes (ginkgolide A, B, C and J)	Microgranules	101

drug leakage after 45 days of storage. It was also found that nanoparticles with more beeswax content in their core exhibited faster drug release as compared with those containing more carnauba wax in their structure<sup>[102]</sup>.

Martins *et al.* carried out the development and validation of a simple reversed-phase HPLC method for the determination of camptothecin in animal organs following administration in SLNs and concluded that the method developed is reliable, precise and accurate and can be used in the determination of CPT amount in rat organ samples after *i.v.*, administration of camptothecin in suspension, in physical mixture with SLN and incorporated in SLN<sup>[103]</sup>.

Tiyaboonchai *et al.* carried out formulation and characterization of curcuminoids loaded SLNs and found that at optimized process conditions, lyophilized curcuminoids loaded SLNs showed spherical particles with a mean particle size of 450 nm and a polydispersity index of 0.4, up to 70% (w/w). The results revealed that after storage in the absence of sunlight for 6 months, the percentages of the remaining curcumin, bisdemethoxycurcumin and demethoxycurcumin were 91, 96 and 88, respectively<sup>[104]</sup>.

Wang *et al.* evaluated the preparation, characterization and antitumor activity studies on emodin loaded solid lipid nanoparticles (E-SLNs). The physicochemical properties of the E-SLNs were investigated by particle size analysis, zeta potential measurement, drug entrapment efficiency (EE), stability and *in vitro* drug release behavior. The E-SLNs showed stable particle size at (28.6±3.1) nm, ideal drug EE and relative long-term physical stability after being stored for 4 months. The drug release of E-SLNs could last 72 h and exhibited a sustained profile, which made it a promising vehicle for oral drug delivery. Moreover, these results suggested that the delivery of emodin as lipid nanoparticles maybe a promising approach for cancer therapy<sup>[105]</sup>.

Kwon *et al.* prepared silk fibroin coated SLNs by an emulsification and solidification method using sodium lauryl sulfate (an anionic surfactant) as a stabilizer and then, the SLN was coated with silk fibroin under an acidic condition by an electrostatic interaction. The silk fibroin coat of nanoparticles was positively charged, so it would strongly interact with negatively charged skins, enhancing the skin permeability<sup>[106]</sup>.

Kuchler *et al.* proposed 3D wound healing model and the influence of morphine with SLNs and the results has concluded the acceleration of wound closure, low cytotoxicity irritation and possible prolonged morphine release make SLN an interesting approach for innovative wound management<sup>[107]</sup>.

Yuan *et al.* investigated the cellular uptake of SLNs and cytotoxicity of encapsulated paclitaxel in A549 cancer cells. The order of cellular uptake ability was glycerol tristearate SLN > monostearin SLN > stearic acid SLN > compritol 888 ATO SLN (ATO888 SLN). Furthermore, the cellular cytotoxicities of paclitaxel were highly enhanced by the encapsulation of lipid matrix. The PEG and folate modified SLN could enhance the cellular uptake of SLN and the cellular cytotoxicity of drug by the membrane disturb ability of PEG chains on the SLN surface and the improved endocytosis mediated by folate receptor<sup>[108]</sup>.

Chen *et al.* evaluated the SLNs as the topical carrier for epidermal targeting of podophyllotoxin (P-SLN). The results had showed the penetration of P-SLN with low particle size into stratum corneum along the skin surface furrow and the consequent controlled release of podophyllotoxin might lead to the epidermal targeting. Furthermore, P-SLN provides a good epidermal targeting effect and may be a promising

carrier for topical delivery of podophyllotoxin<sup>[109]</sup>.

Jenning *et al.* evaluated the potential use of solid lipid nanoparticles in dermatology and cosmetics, glyceryl behenate SLN loaded with vitamin A (retinol and retinyl palmitate) and incorporated in a hydrogel and o/w-cream were tested with respect to their influence on drug penetration into porcine skin. The results had showed that the transepidermal water loss and the influence of drug free SLN on retinyl palmitate uptake exclude pronounced occlusive effects. Therefore enhanced retinyl palmitate uptake should derive from specific SLN effects and is not due to non-specific occlusive properties<sup>[110]</sup>.

Atal *et al.* worked on biochemical basis of enhanced drug bioavailability by piperine. The study was aimed at understanding the interaction of piperine with enzymatic drug biotransforming reactions in hepatic tissue. They found that piperine shows little discrimination between different cytochrome P-450 forms and is a non-specific inhibitor of drug metabolism. Piperine strongly inhibited the hepatic arylhydrocarbon hydroxylase and UDP glucuronyl transferase activities when orally administered to rats. The results of the experiment demonstrated that piperine is a potent inhibitor of drug metabolism<sup>[111]</sup>.

Singh *et al.* found piperine in both long pepper and black pepper as the potent bioenhancer. Rifampicin transcription activity is augmented several fold by piperine against *Mycobacterium smegmatis*. Even at higher concentration of 50 mg/mL, piperine alone shows no inhibitory effect for the growth of *M. smegmatis* but increases the inhibitory potential of rifampicin when given with it in ratio of 24:1 at the lower concentration of 0.125–0.5 mg/mL. The binding ability of rifampicin to RNA polymerase is enhanced by piperine<sup>[112]</sup>.

Chanda *et al.* carried the acute and sub-acute toxicity study and chemical characterization of *trikatu* in Charles Foster rats for safety profiling. Their studies showed that in acute toxicity experiment *trikatu* was well tolerated by the animals under study and no significant changes were observed in morbidity, mortality, gross pathology, vital organ weight, gain in weight, alongwith haematological count and other necessary parameters<sup>[113]</sup>.

Karan *et al.* studied the effect of *trikatu* on the pharmacokinetic profile of indomethacin in rabbits. The results showed that *trikatu* enhanced the absorption of indomethacin which was supposed to be the result of an increase in the gastrointestinal blood flow and an increased rate of transport across gastrointestinal mucosa<sup>[114]</sup>.

Bhat *et al.* carried studies on the metabolism of piperine. They observed that the highest concentration in the stomach and the small intestine was attained at 6th hour. Traces of piperine were detected in the spleen, kidney and serum from 0.5 hour to 24 hour<sup>[115]</sup>.

Singh *et al.* studied the alteration of pharmacokinetics of oxytetracycline following oral administration of *P. longum* in hens. Their studies revealed that the prior administration of *P. longum* increases total duration of antimicrobial action and enhances the therapeutic efficacy of oxytetracycline in poultry birds. There was reduction in loading and maintenance dose and thus the subsequent side effects<sup>[116]</sup>.

Kang *et al.* studied the bioavailability enhancing activities of natural compounds from medicinal plants. They found *trikatu* as an essential ingredient of many ancient prescriptions and formulations and that it played an important role in increasing drug bioavailability when given orally. They concluded that co-administration of natural compounds is one of the promising approaches for increasing bioavailability of drugs<sup>[117]</sup>.



Pattanaik *et al.* evaluated the effect of simultaneous administration of piperine on plasma concentration of carbamazepine twice daily in epileptic patients undergoing carbamazepine monotherapy. They observed that piperine could significantly enhance the oral bioavailability of carbamazepine. The mechanism of action was possibly by decreasing the elimination or by increasing its absorption. They concluded that piperine significantly increased the mean plasma concentrations of carbamazepine in both dose groups<sup>[118]</sup>.

Bhutani *et al.* investigated antidepressant effect of curcumin with piperine. They concluded that the combination of piperine with curcumin showed quite significant potentiation of its anti-immobility, neurotransmitter enhancing (serotonin and dopamine) and monoamine oxidase inhibitory effects as compared to curcumin effect<sup>[119]</sup>.

Kulkarni *et al.* found that there was potentiation of antidepressant activities when piperine was administered simultaneously with curcumin. This approach was useful in the management of depression<sup>[120]</sup>.

Nirala *et al.* Evaluated the effect of piperine individually and in combination with tiferon against beryllium induced biochemical alteration and oxidative stress. They found that the combination of tiferon with piperine could reverse all the variables significantly towards the control<sup>[121]</sup>.

Zhao *et al.* studies concluded that gallic acid exerts a synergistic effect when administered with piperine. This provided a more pronounced therapeutic potential in reducing beryllium-induced hepatorenal dysfunction and oxidative stress consequences. They observed that individual administration of gallic acid and piperine moderately reversed the altered biochemical variables. On the other hand the combination of these was found to completely reverse the beryllium-induced biochemical alterations and oxidative stress consequences<sup>[122]</sup>.

Kasibhatta *et al.* studied the influence of piperine on the pharmacokinetics of nevirapine under fasting conditions. The study was randomized, crossover and placebo controlled. They administered piperine or placebo to healthy adult males for 6 days. On day 7 piperine or placebo was administered with nevirapine. Blood samples were collected post-dose. The results of the study showed that there was an enhanced bioavailability of nevirapine when administered with piperine<sup>[123]</sup>.

Durgaprasad *et al.* evaluated the effect of oral curcumin (500 mg) with piperine (5 mg) on the pain, and the markers of oxidative stress in patients with tropical pancreatitis for 6 weeks. There was a significant reduction in the erythrocyte malonyldialdehyde levels following curcumin therapy in comparison to placebo administration, with a significant increase in glutathione levels<sup>[124]</sup>.

Lambert *et al.* reported that piperine coadministered with (–)-epigallocatechin-3-gallate to male CF-1 mice increased the plasma C(max) and area under the curve by 1.3-fold compared to mice treated with epigallocatechin-3-gallate only. The results appeared such due to inhibition of glucuronidation and gastrointestinal transit<sup>[125]</sup>.

Vladimir *et al.* studied the relative bioavailability of different doses of coenzyme Q10 simultaneous administered with piperine or placebo in healthy adult male volunteers. The results were studied for single-dose experiment or in separate experiments for 14 and 21 days. When compared with coenzyme Q10 plus placebo the result of single and the 14th day dose study indicated smaller, but no significant increase in plasma concentration. Compared to coenzyme Q10 plus placebo supplementation of higher dose coenzyme

Q10 with piperine for 21 days produces a statistically different approximately 30% greater, area under the plasma curve<sup>[126]</sup>.

Vladimir *et al.* studied the effect of simultaneous administration of piperine on serum concentration of  $\beta$ -carotene in healthy volunteers for 14-days. The results of the study indicated a significant increase in serum  $\beta$ -carotene concentration when supplemented with piperine in comparison to  $\beta$ -carotene plus placebo, respectively. They found that there was 60% increase in area under curve of  $\beta$ -carotene plus piperine when compared with  $\beta$ -carotene plus placebo<sup>[127]</sup>.

Kumari *et al.* encapsulated the plant isolated antioxidant quercitrin on poly-D, L-lactide (PLA) nanoparticles by solvent evaporation method to improve the solubility, permeability and stability of this molecule. The size of quercitrin-PLA nanoparticles is (250±68) nm. The encapsulation efficiency of nanoencapsulated quercitrin evaluated by HPLC and antioxidant assay is 40%. The *in vitro* release kinetics of quercitrin under physiological condition reveals initial burst release followed by sustained release. These properties of quercitrin nanomedicine provide a new potential for the use of such less useful highly active antioxidant molecule towards the development of better therapeutic for intestinal anti-inflammatory effect and nutraceutical compounds<sup>[128]</sup>.

Niraimathi *et al.* used the aqueous extract of *Alternanthera sessilis* L. (*A. sessilis*) (Amaranthaceae) in producing silver nano particles (AgNPs) from silver nitrate. The AgNPs obtained was characterized by UV-Visible spectroscopy, FT-IR spectroscopy, SEM, Zeta sizer and TG-DSC. SEM images which revealed the presence of various shapes and sizes. FT-IR spectrum showed the AgNPs having a coating of proteins indicating a dual role of bio-molecules responsible for capping and efficient stabilization of the silver nanoparticles. Presence of impurities and melting point profile were screened by TG-DSC analyzer. AgNPs were synthesized from the silver nitrate through the reducing power of ascorbic acid present in *A. sessilis* leaves<sup>[129]</sup>.

Sahni *et al.* provided a concise incursion on the current pharmacotherapies for Alzheimer's disease besides reviewing and discussing the literature on the different drug molecules that have been successfully encapsulated in nanoparticles. Some of them have been shown to cross the blood brain barrier (BBB) and have been tested either for diagnosis or treatment of Alzheimer's disease. Finally, the route of nanoparticles administration and the future prospects had also been discussed<sup>[130]</sup>.

Aromal *et al.* developed a new synthesis method for monodispersed gold nanocrystals using cheap and nontoxic chemicals, environmentally benign solvents and renewable materials. The nanoparticles have been characterized by UV-Visible spectroscopy, transmission electron microscopy (TEM), X-ray diffraction (XRD) and FTIR analysis. The high crystallinity of nanoparticles is evident from bright circular spots in the SAED pattern and peaks in the XRD pattern. The synthesized gold nanoparticles show good catalytic activity for the reduction of 4-nitrophenol to 4-aminophenol by excess NaBH<sub>4</sub> and found to exhibit size dependent catalytic property, the smaller nanoparticles showing faster activity<sup>[131]</sup>.

Khalil *et al.* conducted the biological synthesis of gold nanoparticles (AuNPs) of various shapes (triangle, hexagonal, and spherical) using hot water olive leaf extracts as reducing agent. The size and the shape of gold nanoparticles are modulated by varying the ratio of metal salt and extract in the reaction medium. The nanoparticles obtained are characterized by UV-Vis spectroscopy, photoluminescence,

TEM, XRD, FTIR spectroscopy and thermogravimetric analysis. The TEM images showed that a mixture of shapes (triangular, hexagonal and spherical) structures was formed at lower leaf broth concentration and high pH, while smaller spherical shapes were obtained at higher leaf broth concentration and low pH<sup>[132]</sup>.

Jeevitha *et al.* aimed to engineer a biodegradable [chitosan (CS) and poly (lactic acid) (PLA)] as anthraquinone carrier with nanometer dimensions and to evaluate the anticancer potency of the prepared CS/PLA–AQ nanoparticles in human carcinoma (HepG2) cells. The *in vitro* release study showed that these nanoparticles provided a continuous release of the entrapped anthraquinone for 10 days, and the release behavior was influenced by the pH value of the medium thereby making feasible to develop CS–PLA for enhanced and sustained release of anthraquinone. The results also suggested that upon CS/PLA–AQ nanoparticles exposure the cell viability decreased due to apoptosis, as demonstrated by the formation of apoptotic bodies, sub–G1 hypodiploid cells, and DNA fragmentation. Henceforth, CS/PLA–AQ nanoparticles demonstrated a strong antitumor activity *in vitro* by reducing cell viability, inducing cell necrosis, decreasing the negative surface charge and mitochondrial membrane potential, and fragmenting DNA<sup>[133]</sup>.

Parhi *et al.* reported that nanotechnology–based combination drug delivery to tumor tissues has emerged as an effective strategy by overcoming many biological, biophysical and biomedical barriers that the body stages against successful delivery of anticancer drugs. The sustained, controlled and targeted delivery of chemotherapeutic drugs in a combination approach enhanced therapeutic anticancer effects with reduced drug associated side effects. In this article, we have reviewed the scope of various nanotechnology–based combination drug delivery approaches and also summarized the current perspective and challenges facing the successful treatment of cancer<sup>[134]</sup>.

Rajendran *et al.* loaded the ethanolic extract of *Ocimum sanctum* inside the sodium alginate chitosan nanoparticles by cation induced controlled gellification method and finished on cotton fabric by pad dry cure method. The average particle size of the nanoparticles was calculated using dynamic light scattering technique. The antimicrobial activity of the fabrics was assessed by using the standard AATCC technique (AATCC 100). The quantitative tests proved that cotton fabrics finished with the methanol extract of *Ocimum sanctum* loaded nanoparticles possessed remarkable antibacterial activities with excellent wash durability. The study revealed that the herb encapsulated nanoparticle could act as a biocontrol agent against bacteria in fabrics<sup>[135]</sup>.

Yallapu *et al.* focused on the design and development of nanoparticles, self–assemblies, nanogels, liposomes and complex fabrication for sustained and efficient curcumin delivery as it has proven to be a modulator of intracellular signaling pathways that control cancer cell growth, inflammation, invasion and apoptosis, revealing its anticancer potential. The anticancer applications and clinical benefits of nanocurcumin formulations was also discussed. Only a few novel multifunctional and composite nanosystem strategies offer simultaneous therapy as well as imaging characteristics. We also summarize the challenges to developing curcumin delivery platforms and up–to–date solutions for improving curcumin bioavailability and anticancer potential for therapy<sup>[136]</sup>.

Chaudhary *et al.* provided a concise review on an account of the main issues emanating from applications of nanotechnologies in food and related sectors with a particular

reference to developing countries<sup>[137]</sup>.

Li *et al.* reviewed that nanoparticle therapeutics, comprising of drugs, nucleic acids or proteins in association with a carrier, have emerged as safe and efficient systems in the treatment of the respective liver diseases and described the targeting strategies employed in relation to liver anatomy and disease etiologies, summarized recent advances in the field and discussed the challenges and future perspectives for the effective treatment of liver diseases using polymer– and lipid–based nanoparticle therapeutics<sup>[138]</sup>.

Jain *et al.* studied the advances in understanding the aetiology, epidemiology and microbiology of periodontal pocket flora in revolutionising the therapeutic strategies for the management of periodontal disease progression and summarised the recent developments in the field of intra–pocket drug delivery systems and identifies areas where further research may lead to a clinically effective intra–pocket delivery system<sup>[139]</sup>.

Suryawanshi *et al.* reviewed that the bioavailability can be improved by phytosomal drug delivery system, which can enhance the rate and the extent of drug absorption across the lipoid biomembrane, which have been found promising for better and effective delivery of drug and providing much appropriate systematic drug delivery<sup>[140]</sup>.

Priprem *et al.* compared and evaluated oral quercetin (300 mg/kg body weight/day) was compared with oral and intranasal quercetin liposomes (20 µg/day). Anxiolytic and cognitive–enhancing effects of quercetin, conventional and liposomal, were subjected to elevated plus maze and Morris water maze tests, respectively. Both conventional and quercetin liposomes showed anxiolytic and cognitive–enhancing effects. A lower dose and a faster rate were observed with intranasal quercetin liposomes when compared with oral quercetin, conventional and liposomal and the intranasal quercetin liposomes are effective in the delivery of quercetin to the central nervous system<sup>[141]</sup>.

Yilmaz *et al.* synthesised silver nanoparticles employing a shadow–dried *Stevia rebaudiana* leaf extract in AgNO<sub>3</sub> solution. TEM and XRD inspections indicate that nanoparticles are spherical and polydispersed with diameters ranging between 2 and 50 nm with a maximum at 15 nm. Ultraviolet–visible spectra recorded against the reaction time confirms the reduction of silver nanoparticles indicating that the formation and the aggregation of nanoparticles take place shortly after the mixing, as they persist concurrently with characteristic times of 48.5 min and 454.5 min, respectively. Proton nuclear magnetic resonance spectrum of the silver nanoparticles reveals the existence of aliphatic, alcoholic and olefinic CH<sub>2</sub> and CH<sub>3</sub> groups, as well as some aromatic compounds but no sign of aldehydes or carboxylic acids. Infrared absorption of the silver nanoparticles suggests that the capping reagents of silver and gold nanoparticles reduced in plant extracts/broths are of the same chemical composition of different ratios<sup>[142]</sup>.

Philippi *et al.* reviewed the concept of telomerase and telomerase inhibition in cancer therapy and also aimed to provide an overview of the different currently known telomerase inhibitors. Finally, the biopharmaceutical limitations of these molecules are discussed as well as the possibilities to overcome those limits by novel drug carrier systems and formulation approaches<sup>[143]</sup>.

## 14. Conclusion

Bioenhancers constitute an innovative concept, the

discovery of which was based on a traditional system of Indian medicine (as mentioned by Charaka, Sushruta and other apothecaries in traditional system of medicine). The concept would be useful in decreasing in drug cost, toxicity, and other adverse effects, and thus may ultimately have a positive influence on the national economy (as desired by WHO) of our/one's country. It satisfies all necessary criteria to be considered as an ideal drug. It is safe, effective, economical, easily procured, non-addictive, and has a widely-based effect on several classes of drug. New drug development technologies are concerned about the economics of drug development. Drug discovery process has been highly aided by Ayurveda through reverse pharmacology with new means of identifying active compounds and reduction of drug development cost. The researches are now aimed at methods of reduction of drug dosage and thus drug treatment cost making treatment available to a wider section of the society including the financially challenged. Hence, it has been proved that novel drug delivery system of herbal as well as of chemical origin has been used to increase the bioavailability of the compounds or their respective constituents (in case of herbal extracts) which has been mentioned in following reported studies related to curcuminoids, silymarin, flavonoids, terpenoids *etc.*

### Conflict of interest statement

We declare that we have no conflict of interest.

### Acknowledgement

The authors are thankful to Prof. (Dr.) Shubhini A. Saraf and to AICTE – MODROBS Grant (Grant No. 8024/RID/BOR/MOD-458/2009-10), for making this review work possible.

### Comments

Exhaustive analysis of the literature available has been carried out by the authors and their team. Almost all the publications based on the topic had been covered. The researchers are now aimed at methods of increasing the bioavailability of various plant extract which has been available to a wider section of the society. Hence, it has been proved that novel drug delivery system of herbal as well as of chemical origin has been used to increase the bioavailability of the compounds or their respective constituents (as in case of herbal extracts).

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