Appraisal of Bioenhancers in Improving Oral Bioavailability: Applications to Herbal Medicinal Products

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Authors’ contributions

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ABSTRACT

The oral route of administration is associated with some challenges such as poor aqueous solubility and low intestinal permeability of many active pharmaceutical ingredients resulting in decreased drug absorption and subsequent poor bioavailability. In recent years, research on bioenhancers has started receiving increased attention and this approach can complement the traditional methods of solubility enhancement. Bioenhancers boost the bioavailability of drugs when co-administered at low doses with the drug. A large variety of compounds have been clearly demonstrated to possess significant bioenhancing activity with different mechanisms of action. Some compounds considered as bioenhancers isolated from plants include piperine, gallic acid, niazipiridine, sinomenine, genistein, and lysergol. There are several reports of herbal medicinal products (HMPs) that require large doses to be therapeutically effective and some studies have identified that the active compounds in such products have poor bioavailability. Thus, there is every need to optimise dosage formulations of HMPs. The application of the concept of bio-enhancement and knowledge of their mechanism of action can lead to the selective use of suitable bioenhancers.
resulting in reduction in therapeutic dose of the HMP, thus reducing the possibilities of toxicity. This
review was aimed at updating knowledge on different natural bioenhancers and also provides an
overview of currently marketed HMPs containing bioenhancers. The article highlights different
strategies that can be employed to improve the bioavailability of HMPs. The bioactive constituents
of the HMP were identified and facts on their physicochemical properties, metabolic fate, as well as
factors that impact on their gastrointestinal absorption, were examined with a view to providing
information to serve as a guide in developing suitable bioavailability enhancement strategies for
other HMPs.

Keywords: Bioavailability improvement; bioenhancers; herbal medicinal products.

1. INTRODUCTION

1.1 Bioavailability and Biopharmaceutic Classification Systems (BCS)

For a drug to undergo absorption, it must be available as an aqueous solution at the site of
absorption. This implies that aqueous solubility and dissolution rate are very important properties
of any drug and impact on its oral bioavailability [1]. A major challenge in the development of
formulations of poorly water-soluble drugs is how to increase their bioavailability and it is reported
that about 70% of all new chemical entities (NCE) have poor water solubility and fail to have
commercial viability due to their limited bioavailability [2]. The drug molecules have to traverse biological membrane at the absorption site to enter the systemic circulation. Hence, the gastrointestinal permeability of the drug is also a fundamental factor that contributes to determining the rate and extent of drug absorption and its bioavailability [3]. The importance of solubility and permeability in controlling bioavailability has been demonstrated in their being used to construct the Biopharmaceutic Classification Systems (BCS). BCS is a scientific framework for classifying a drug substance based on its solubility and intestinal permeability and they have been found useful in combination with dissolution rate data to predict absorption profile of drug products [4-6]. It is important to consider the BCS class of a drug substance to be able to make an informed judgment on the best approach to follow when improvement of bioavailability of a drug is desired. According to United States Food and Drug Administration (USFDA) BCS guidance, a drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1-6.8 at 37 ± 1°C [7]. The drug permeability may be determined directly from the extent of intestinal absorption of a drug substance in humans. It can also be estimated indirectly from the measurements of the rate of the mass transfer across the intestinal membranes in vitro or by using in vivo models. A drug substance is considered to be highly permeable when the systemic bioavailability or the extent of absorption in humans is determined to be 85 percent or more of an administered dose based on a mass balance determination (along with evidence showing stability of the drug in the GI tract) or in comparison to an intravenous reference dose [7].

The BCS class 1 (high solubility/high permeability) usually do not have bioavailability problems since their absorption is neither dissolution nor permeability rate-limited. However, Active Pharmaceutical Ingredients (APIs) in this BCS class can only enjoy bioavailability waiver if they satisfy all the requirements of high solubility, high permeability and rapid dissolution [7]. Examples of drug substances in this class include diltiazem, metoprolol, paracetamol, propranolol etc [8]. The BCS class II drugs have low aqueous solubility and high permeability, hence, dissolution process is the rate-limiting step in the drug absorption process. Bioavailability of this class of drugs can be enhanced by using techniques that increase the solubility and dissolution rates of the compound. Studies from our laboratories and by several other investigators indicate that different methods are used for the improvement of the solubility of poorly water-soluble drugs and these include micronisation, crystal form modification, salt formation, use of surfactant, complexation with cyclodextrin and other complexing agents, solid dispersion, and others [3,9-12]. With the advancement in technology, novel techniques such as cryogenic technology, nano-suspension, and supercritical processing have also been developed for solubility enhancement [1,13-16]. It is noteworthy that several researches on solubility enhancement have been focused on the BCS class II drugs [17,18]. For the BCS class III drugs (High solubility/low permeability), there
can be bioavailability waivers for the APIs that have high solubility and rapid dissolution rate. In addition, the test product formulation should be qualitatively the same and quantitatively very similar [7]. However, since the absorption of some APIs in this class can be limited by its rate of intestinal permeability, the use of absorption enhancers or bioenhancers which can improve their permeability has the potential of enhancing bioavailability of the drug. In the case of BCS class IV compounds (low solubility/low permeability), the drug absorption is both dissolution and intestinal permeability rate-limited. The bioavailability of this class of drug substances may be achieved through enhancement of solubility and dissolution rate in addition to the use of absorption enhancers. Examples of drugs in this class include ritonavir, saquinavir, taxol, cyclosporine A and several others [8].

1.2 Bioavailability with Bioenhancers

It is evident from the BCS that the classes III and IV drugs have low intestinal permeability, thus, approaches that can increase the permeability of these compounds are likely to enhance their bioavailability. The use of bioenhancers can be regarded as an innovative concept. Bioenhancers are agents or substances that boost the bioavailability of drugs when co-administered at low doses with the drug. An ideal bioenhancer should be safe, effective, readily available and economical. In addition, it should not produce its own pharmacological effects at the dose used; should be rapid-acting with predictable and reproducible activity and should be compatible with other APIs [19,20]. When used in a judicious manner bioenhancers can lead to reductions in drug dosages due to enhanced bioavailability, with resultant decreases in drug treatment cost, toxicity and adverse effect profiles [21]. From historical viewpoint, bio-enhancement originated from Ayurvedic medicine as reported by Bose in 1929 who first described the use of a condiment, long pepper, to improve the antiasthmatic effect of the leaf of Adhatodavasica species [22].

1.3 Bioavailability and Herbal Medicinal Products

From time immemorial, phytomedicine has been playing an important role in pharmacotherapy and presently, about 50 percent of useful drugs are obtained from natural sources [23]. Several reports indicate that the use of Herbal Medicinal Products (HMPs) as part of Complementary and Alternative Medicines is very widespread in large sections of the population in developing countries [24,25]. Also, as complementary and alternative medicines are now becoming popular in developed countries [26,27], reports show that over the past two decades, there has been an increased prevalence in use of HMPs in these countries [28,29]. The revival of interest in HMPs has been ascribed to a number of factors such as the perception that herbal products are safer because they are natural in origin. Other reasons include the cost-effectiveness and the belief that herbal medicines might be effective in the treatment of certain diseases where conventional therapies have proven to be ineffective [27,30,31]. In spite of their significant therapeutic effects and less adverse effects profiles, there are numerous cases of herbal products with remarkable in vitro activities but with disappointingly poor in vivo efficacy. These are revealed through animal and clinical trial studies conducted on HMPs indicating that the herbal drugs have poor bioavailability [32,33]. Thus, several plant extracts and phytoconstituents demonstrate reduced in vivo actions due to the inappropriate molecular size, poor aqueous solubility and/or poor intestinal permeability of the bioactive constituents resulting in decreased absorption and consequently poor bioavailability. For example, extract of the plant Azadirachta indica, which is widely used in indigenous medicine for the treatment of malaria exhibits high in vitro activity against various strains of Plasmodium falciparum but required very high doses (e.g. 800 mg/kg body weight) to exhibit significant in vivo activity [34,35]. Similarly, Silybum marianum commonly known as milk thistle has Silymarin as the major bioactive compound isolated from its seed which has numerous applications including use for the oral therapy of chronic liver disorder. But, its efficacy is limited by poor aqueous solubility, resulting in poor bioavailability [36]. In addition to other techniques used for improving solubility and bioavailability of APIs, it has been demonstrated that the efficacy of HMPs with poor in vivo activity can be improved by formulating the product with a herbal bioenhancer [37]. The need for bioenhancers is especially applicable when the bioactive constituents have limited intestinal permeability. In essence, a better understanding of the physicochemical characteristics of the bioactive constituents of HMPs will assist in designing a formulation with optimal bioavailability.
The objective of this review was to update knowledge on different natural agents being used as bioenhancers and to discuss their possible mechanisms of action with the overall aim of providing an insight into how these pharmacological advances can be applied in optimization of bioavailability of formulations of HMPs. Also, the article highlights different other strategies that can be employed to improve the bioavailability of HMPs. Since herbal medicine is increasingly playing a significant role in the healthcare industry, it is appropriate that the products also receive due attention to the orthodox medicines.

2. ROLE OF BIOENHANCERS

2.1 Classification of Bioenhancers

A large variety of both natural and synthetic compounds have been clearly demonstrated to possess significant bioenhancing activity and they have different mechanisms of action [38-40]. Bioenhancers are categorized either based on their origins (natural-from plants and animals; and synthetic), chemical classes or mechanism of actions. Some compounds considered as bioenhancers isolated from plants include piperine, gallic acid, niaziridine, sinomenine, genistein, and lysergol. Apart from the isolated molecules, whole plant or parts of the plant are also used as bioenhancers. Examples of parts of plants used as bioenhancers include the rhizomes of Zingiber officinale and the seeds of Carum carvi [16]. Piperine is the world’s first bioavailability enhancer first reported in 1979 and there are currently several reports on its bioavailability enhancement of various drugs and nutraceuticals [39,40]. Since bioenhancers have different mechanisms of bioavailability improvement, it is pertinent to clarify that the term ‘absorption enhancers’ is used for a class of bioenhancers that promote bioavailability by specifically enhancing the intestinal permeability of the drug [41]. Based on their mechanisms of action, there are three major classes of bioenhancers [38,42] and these include:

(a) Regulators of GIT functions: Aloe vera, Niaziridin, Zingiber officinale (Ginger), Glycyrrhizin (from Liquorice).
(b) Inhibitors of cytochrome P450: Piperine, Naringin, Gallic acid and its esters.
(c) Inhibitors of P-glycoprotein (P-gp) and other efflux pumps: Piperine, Carum carvi, Genistein, Sinomenine, Naringin.

2.1.1 Inhibitors of cytochrome P450 and P-gp

Piperine (1-piperoyl piperidine) is an alkaloidal component of Black pepper (Piper nigrum) and long pepper (Piper longum). The fruits of these two herbs generally contain volatile oil (1 – 2.5%) and total alkaloids (5 – 9%) with the major alkaloids consisting of piperine, piperdine, and pipperseine. It has been documented that most of the pharmacological properties of the fruits are credited to the piperine [43]. Ethnopharmacological survey indicates that piperine/pepper is commonly used as antirheumatic, analgesic, diuretic, antispasmodic and antiseptic [44] or a preservative and a perfume in some climes. However, when used as a bioenhancer, these pharmacological effects are not relevant.

Studies have established piperine to be useful as a bioenhancer at a low dose of 10-15 mg [45]. This property was first utilized to enhance the bioavailability of rifampicin by more than 50% in an antitubercular regimen [46]. Thus, studies have shown that piperine increases the bioavailability and efficacy of numerous drugs including phenytoin, sulfadiazine, propranolol, carbamazepine, fexofenadine, ampicillin Trihydrate, nevirapine, metronidazole, omeprazole and many other drugs. It was concluded that piperine significantly enhanced the oral bioavailability of these drugs, possibly by decreasing the elimination and/or by increasing its absorption through the inhibition of P-glycoprotein (P-gp) at the gut and kidneys, in addition to inhibition of CYP3A4 and other drug-metabolizing enzymes especially UDP-glucuronosyl transferase (UGT) in the gut [47-53]. Piperine also mediates bioavailability enhancement by enhancing the blood supply in the enteric vessel due to its local vasodilatory effect [54], improvement of lipid solubility through increase in the secretion of bile acid and modification of intestinal epithelial cells [45].

Other herbal bioenhancers that have similar bioenhancing mechanisms of action like piperine include:

(a) Naringin: Naringin is a CYP3A4 inhibitor [55]. It is the major flavonoid glycoside found in grapefruit, apples and onions. Due to its ability to inhibit intestinal CYP3A4 and P-gp, it has been found to enhance the bioavailability of a number of CYP3A4 and P-gp substrates such as paclitaxel, diltiazem, verapamil, saquinavir and cyclosporine A [56,57].

<table>
<thead>
<tr>
<th>Bioenhancer</th>
<th>Classification</th>
<th>Inhibitory Target</th>
<th>Examples</th>
</tr>
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<tr>
<td>Piperine</td>
<td>Inhibitors of cytochrome P450</td>
<td>CYP3A4</td>
<td>Niaziridine, Sinomenine, Genistein</td>
</tr>
<tr>
<td>Naringin</td>
<td>Inhibitors of P-glycoprotein</td>
<td>P-gp</td>
<td>Gallic acid, Nizinidine</td>
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Ethnopharmacological survey indicates that piperine/pepper is commonly used as antirheumatic, analgesic, diuretic, antispasmodic and antiseptic or a preservative and a perfume in some climes. However, when used as a bioenhancer, these pharmacological effects are not relevant.
(b) Gallic acid: Gallic acid is a CYP3A4 inhibitor [58] and its esters like propyl gallate, octyl gallate and lauryl gallate have been demonstrated to increase the bioavailability of orally administered pharmaceutical compounds which are substrates of CYP3A4 [57,58].

(c) Sinomenine: Sinomenine, a monoterpene glucose alkaloid extracted from Sinomenium acutum is known to be a P-gp inhibitor [59]. Co-administration of sinomenine markedly increased the oral absorption of paeoniflorin through a decrease in the efflux transport of the drug by P-gp in the small intestine [59]. Paeoniflorin, used in the treatment of inflammation and arthritic conditions, has a very low oral bioavailability which is in the range of 3 – 4% [60].

(d) Genistein: Genistein, an isoﬂavone found in a number of dietary plants like soyabean (Glycine max) and kudzu (Pueraria lobata), is known to be a P-gp inhibitor [40,61]. The intestinal absorption of paclitaxel, a substrate of P-glycoprotein, was signiﬁcantly augmented when co-administered with genistein [61].

(e) Carum carvi: Carum carvi (family – Apiaceae) also called Caraway/cumin has carvone as its major constituent which is obtained from the dried and crushed seeds. At a dose in the range of 5 – 100 mg/kg body weight, this extract signiﬁcantly enhanced bioavailability of a wide range of drugs of various therapeutic classes including antimicrobial, antileprosy, anti-inﬂammatory, anti-arthritic, cardiovascular, antihistaminics, CNS drugs, antiulcers, nutraceuticals and herbal formulations. Its mode of action is by inhibition of P-gp efflux pump [38,40,62].

2.1.2 Regulators of GIT functions

Ginger, the rhizome of Zingiber ofﬁcinale, has a long history of medicinal use for conditions such as diarrhoea, nausea, and stomach ache, in addition to a range of other pharmacological activities [63,64]. Ginger contains numerous constituents but the major is gingerols which can be converted to shogaols, zingerone, and paradol [65]. These compounds along with the volatile oil constituents have strong effects on GIT mucous membrane resulting in regulating the intestinal function to facilitate absorption [42]. Ginger is used in the range of 10-30 mg/kg body weight as bioenhancer [66]. The extracts of ginger have been found to be selective in their abilities to enhance bioavailability of a wide range of drugs of different therapeutic classes and the enhancement can vary from 20% to 200% [67,68]. These drugs include azithromycin, ketoconazole, erythromycin, cefadroxil, amoxycillin, cloxacillin, rifampicin, ethionamide, zidovudine and fluorouracil [47]. These drugs are not necessarily substrates of particular drug metabolising enzymes or drug transporter systems. Therefore, unlike piperine and other bioenhancers which are inhibitors of CYP3A4 and P-gp, and whose bioavailability enhancement are manifested on drugs that are substrates of these systems, the bioenhancing effect of ginger extract is not predictable.

Other herbal Bioenhancers with action on GIT membrane similar to the effect of ginger include:

(a) Aloe Vera Extract: The gel and whole leaf extracts of Aloe vera have been demonstrated to enhance the oral absorption of vitamin C and vitamin E [69]. The bioenhancing mechanism of action of these products is thought to be attributed to their polysaccharides constituents. Polysaccharides of natural origin such as chitosan act as penetration enhancers through a process of a transient opening of the tight junctions between adjacent epithelial cells. Thus, they are capable of enhancing the intestinal absorption of concurrently administered drugs. It has been shown that the Aloe vera gel and whole leaf extract significantly increased the transport of the macromolecular peptide drug, insulin, across the Caco-2 cell monolayers [70]. Limited information is currently available on the drug absorption enhancement activities of A. vera extracts.

(b) Liquorice: Liquorice is the name given to the root of the plant Glycyrrhiza glabra. The extract of this plant contains a phytoconstituent, Glycyrrhizin, that has been established to have bioenhancing activity. The compound is reported to cause a 2 to 6 fold enhancement in GIT absorption of various drugs such as rifampicin, tetracycline, nalidixic acid, ampicillin and vitamins B1 and B12 [71]. In a study to elucidate the molecular mechanism of bioenhancing action of glycyrrhizin, the influence of the compound on the functional properties of biomembranes was investigated using a
model system of human erythrocytes. Glycyrrhizin produced about 60% increase in the permeability and decreased elasticity modulus of cell membranes even in micromolar concentrations [72]. Structurally, glycyrrhin is a saponin and saponins have surfactant properties that can act on the paracellular route [73]. The absorption enhancing effect of glycyrrhizin is further enhanced in the presence of other enhancers [74].

(c) Nitrile glycosides: Niaziridin and niazirin are nitrile glycosides isolated from the pods of Moringa oleifera (Family - Moringaceae). They have been found to increase the bioavailability of commonly used antibiotics (eg rifampicin, tetracycline and ampicillin), vitamins, and nutrients by facilitating their absorption through the gastrointestinal membrane [47,75]. For example, in a study on the influence of active fraction isolated from pods of Moringa oleifera on pharmacokinetic disposition of rifampicin, the results revealed that co-administration of the extract resulted in significantly increased rifampicin plasma concentrations [76].

3. HERBAL MEDICINAL PRODUCTS WITH BIOENHANCERS

Applications of novel techniques for improvement of bioavailability of drugs have been extended to HMPs and these include herbal liposomal formulations, microspheres, nanoparticles, transfersomes, lipid-based herbal formulations, and other herbal vesicular formulations [77]. In addition, there are studies reporting clear evidence of improvement of oral absorption and bioavailability of HMPs by concomitant use of bioenhancers. The literature is replete with studies indicating bioavailability enhancement of orthodox medicines by bioenhancers [16] but an extensive review of the literature revealed comparatively limited data on the deliberate application of this technique in HMPs with poor bioavailability.

The emphasis of this review is to focus more on the enhancement of bioavailability of HMPs. The bioactive phytoconstituents of the HMP are identified and information on their physicochemical properties, metabolic fate as well as factors that impact on their gastrointestinal absorption are examined. These can serve as guide for the application of the bioavailability enhancement technique to other HMPs with intrinsic poor bioavailability of its active constituents. There are numerous reports of decreased absorption and subsequent poor bioavailability resulting in reduced in vivo activities of several medicinal plant extracts and phytocconstituents. The factors contributing to decreased gastric absorption and subsequent poor bioavailability include the nature of physicochemical properties of the active constituents such as poor aqueous solubility, large molecular weight, excessively high aqueous solubility, instability in the GIT fluid as well as metabolism at the gut epithelial cells and activities of drug transporters [34-36].

3.1 HMPs with Piperine (and Other Bioavailability Improvement Approaches)

3.1.1 Curcumin

Curcumin, commonly called diferuloyl methane, has been identified as the active principle derived from the rhizome (called turmeric) of the herb Curcuma longa. It is a hydrophobic compound that has been used traditionally in the management of a variety of ailments due to its wide spectrum of pharmacological activities [78]. Curcumin has structurally related compounds which are all curcuminoids but are often referred to simply as curcumin and their chemical structures are presented in Fig. 1. Commercially available curcumin generally contains three major curcuminoids: curcumin (77%), demethoxycurcumin (7%) and bisdemethoxycurcumin (3%) [78].

Early studies of the pharmacokinetics of curcumin in animal models have shown that it is poorly absorbed from intestine after oral administration of different doses of the compound [79]. The hydrophobicity of the compound results in its poor aqueous solubility and this class of compounds in the BCS is associated with reduced bioavailability. In a study to determine whether curcumin is a substrate of P-gp and CYP3A isozymes, the compound was co-administered with drugs (celiprolol and midazolam) that are known substrates of these systems in a rat model. Results indicated that the plasma blood levels of celiprolol (a P-gp substrate) and midazolam (substrate of CYP3A) were significantly increased by curcumin, confirming that curcumin is a substrate for both P-gp and CYP3A [80]. Since the mechanisms by which piperine acts as a bioenhancer is by reducing drug metabolism in the gut through
inhibition of CYP3A activity in gut epithelial cells and also by inhibiting P-gp transport system [52], inhibition of these two systems by piperine in gut epithelial cells is expected to lead to increasing in curcumin absorption. This hypothesis was validated in a study on the effect of piperine on the bioavailability of curcumin in which it was demonstrated that concomitant administration of piperine significantly increased the extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects. In humans, the increase in bioavailability was as high as 2000% [81]. Also, there was a potentiation of curcumin antidepressant activity following concomitant administration of this HMP with piperine. This approach has been found useful in the management of depression [82,83]. It is reasonable to project that a poorly absorbed HMP with constituents having similar physicochemical characteristics as curcumin and are also substrates of P-gp and CYP3A4 can be made more bioavailable by concurrent use with piperine.

3.1.2 Rutin

Rutin also known as quercetin-3-rutinosid or sophor is a flavonol glycoside comprising quercetin (a flavanol) and a disaccharide called rutinose (α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranose). The chemical structure is presented in Fig. 1. It is found in a wide variety of plants including many citrus fruits and is often sold as an herbal supplement. Quercetin, the active moiety of rutin has been reported to exert numerous pharmacological activities including antidiabetic, anti-inflammatory, antioxidant, cardiovascular, and it has been used therapeutically to decrease capillary fragility and for management of many chronic diseases [84-86].

Considering the size and polarity of flavonoids, some medicinal chemistry rules would predict difficulty in their ability to cross bio-membranes. Thus, generally, flavonoids are poorly absorbed from the small intestine. The high molecular
weight of rutin (664.58) also limits the intestinal permeability of the compound. Studies have shown that trans-epithelial transport of rutin is poor and mainly by passive diffusion [87,88]. For this class of compounds, techniques that enhance solubility and intestinal permeability are promising approaches to bioavailability improvement. The oral bioavailability of rutin in human studies showed that the compound is poorly orally absorbed with only 20 – 30% of the dose absorbed [89]. There are numerous reports on studies aimed at improving the bioavailability by applying various excipients and techniques including use of cyclodextrin complexation, surfactants, nano-phytosomes, chitosan, and nanoemulsion [20,90-92].

A contribution to the poor oral absorption of rutin is the metabolism of the compound in the gut. The microflora in lower gut hydrolyzes rutin to quercetin and isoquercetin [93]. But, the enzyme Uridine Diphosphate-Glucoronosyl-Transferase (UGT) conjugates the part of the free quercetin with glucuronide producing a bulky and inert adduct which is un-absorbable, hence, reducing the extent of absorption of quercetin [94]. Since piperine has been shown to be an inhibitor of UGT [51], this bioenhancer was demonstrated to improve the neurocognitive efficacy of quercetin in mice [95] and this is an indication of enhanced bioavailability of quercetin by piperine. Studies have also shown that piperine can enhance the antioxidant and anti-inflammatory properties of quercetin, and quercetin exhibited stronger neuroprotective effects when given in combination with piperine [96]. An in vitro study demonstrated that piperine enhanced antioxidant effect of rutin and the authors suggested that the findings provide more insight into the mechanism of the hepato-protective action of rutin [97]. It is not likely that piperine enhanced bioavailability and hence the efficacy of rutin or quercetin through modulating P-gp activity because rutin and related compounds have been shown not to be substrates for efflux transporters [89]. From the foregoing, the bioavailability of HMPs containing phytoconstituents with similar physicochemical properties and metabolic fate as rutin might be expected to be enhanced when co-administered with piperine.

3.1.3 Echinacea

Preparations from the genus Echinacea which are from Echinacea species (Echinacea angustifolia, Echinacea pallida and Echinacea purpurea) are among the most widely used herbal medicines and have a long history of medicinal use for a variety of conditions especially in the prevention and treatment of upper respiratory tract infections attributed to the immunostimulatory and anti-inflammatory properties of the HMP. The fresh or dried underground parts (roots, rhizomes) of these species are used and the marketed echinacea products may contain one or more of these three species [98-100]. The major constituents that are responsible for the bioactivities of this HMP are hydrophilic components which include caffeic acid derivatives (cichoric acid, echinacoside, and chlorogenic acid) and lipophilic components which are alklyamides [98]. Their chemical structures are presented in Fig. 2.

Studies to enhance the bioavailability of echinacea constituents have been reported. Due to the hydrophilicity of caffeic acid derivatives, their intestinal permeability has been shown to be poor while the lipophilic alklyamides diffuse rapidly [101]. Echinacoside, representing caffeic acid derivatives is a substrate of P-gp and inhibition of this transporter by verapamil resulted in the oral bioavailability enhancement of the compound [102]. Also, the essential oils in clove oil acting as absorption enhancers augmented the intestinal absorption of echinacoside [102]. Since these caffeic acid derivatives are substrates of P-gp and CYP3A4 [102,103], it is expected that absorption of these compounds may be enhanced by piperine which inhibits the activities of this transporter and isoyme at the gut epithelial. This assumption was validated by studies indicating augmentation of bioavailability of echinacea extract by concurrent administration of piperine [42].

3.1.4 Boswellia

Boswellia serrata (Family: Burseraceae) is a deciduous middle sized tree mostly concentrated in parts of Asia and Africa. The dried exudate from the bark of this tree is an oleo-gum-resin which has a wide range of pharmacological activities and is reported to be useful in the treatment of bronchitis, asthma, cough, inflammatory conditions and various intestinal problems [104-106]. The major fraction of the gum-resin consists of terpenoids of which the biologically active phytoconstituent is boswellic acid which is a pentacyclic triterpene acid [107]. α- and β-Boswellic acids were the first to be isolated followed by several other of its derivatives such as 3-acetyl-α-boswellic acid, 3-acetyl-β-boswellic acid, 11-keto- β-boswellic acid and 3-acetyl-11-keto- β-boswellic acid [106]. Some of these structures are presented in Fig. 3.
Dodeca-2E,4E,8Z,10Z-tetraenoic acid isobutylamide (A1); Dodeca-2E,4E-dienoic acid isobutylamide (A2); Undeca-2E-en-8,10-diynoic acid isobutylamide (A3)

Cichoric acid

Chlorogenic acid

Echinacoside

Fig. 2. Chemical structures of some of the bioactive constituents of Echinacea

Being pentacyclic triperpenes, boswellic acid and its derivatives are lipophilic and the poor aqueous solubility results in low oral bioavailability of these compounds. In addition, the keto derivatives of boswellic acid undergo extensive first pass metabolism and this contributes to the low oral bioavailability [108, 109]. Many attempts have been made to produce drug delivery systems with improved absorption such as loading boswellic acids into liposomes, solid lipid nanoparticles as well as delivery as niosomes, phytosomes and nano-micelles [110].

Studies indicate that CYP3A4 plays a predominant role in the hydroxylation reaction of keto-boswellic acid in the GIT of humans [111] and this contributes to a reduction in drug absorption. Coadministration with piperine has the potential to improve the bioavailability of keto-boswellic acid as it is an inhibitor of CYP3A4. It has been demonstrated that piperine significantly enhanced the bioavailability of boswellia extracts when concurrently administered [112]. This observation can also be applied to other HMPs containing phytoconstituents with similar metabolic fate.
3.1.5 Ginkgo Biloba

*Ginkgo biloba* is a large tree originally native to China but it is now cultivated worldwide. The leaf extract has been used in traditional medicine for centuries to treat circulatory disorders, asthma, tinnitus, vertigo, and cognitive problems, and it is one of the most commonly taken phytomedicines globally [113,114]. The pharmacological properties of this HMP are attributed to its constituents of terpenoids, flavonoids and proanthocyanidins [115]. These active components have been identified as bilobalide, ginkgolides A, B, C, quercetin, kaempferol, rutin hydrate, and isorhamnetin [116]. Their chemical structures are depicted in Fig. 4.

As earlier highlighted with quercetin, flavanoids have poor oral absorption. Thus, different approaches have been investigated for improvement of the bioavailability of Ginkgo extract and these included the use of phospholipid complexes and solid dispersions [117]. The major pathway of metabolism of flavonoids in humans is hydrolysis in the intestinal microflora followed by phase II conjugation reaction where UGTs are the major contributors [118]. Based on the knowledge of mechanisms of bioenhancing activity of piperine, being an inhibitor of UGT, a concurrent administration with piperine is expected to enhance the oral absorption of the Ginkgo flavanols. In addition, studies have shown that Ginkgo flavonoids quercetin, kaempferol and isorhamnetin are substrates of P-gp. This efflux pump contributes to limiting the bioavailability of the flavanols [119]. Since piperine also acts by inhibiting activity of P-gp, this is an additional pathway through which it can enhance bioavailability of Ginkgo flavanols. These expectations have been validated in studies which demonstrated that piperine significantly enhanced the bioavailability of Ginkgo extracts when concurrently administered [112].
Ginkgolides A, B and C

\[ \begin{align*}
R_1 \quad R_2 \quad R_3 \\
A & \quad OH \quad H \quad H \\
B & \quad OH \quad OH \quad H \\
C & \quad OH \quad OH \quad OH
\end{align*} \]

Kaempferol

Isorhamnetin

Bilobalide

Fig. 4. Chemical structures of the major bioactive constituents of Gingo biloba extracts

The physicochemical properties and metabolic fate of the Ginkgo terpene lactones (bilobalide and ginkgolides) are different from those of the flavanols. The intestinal absorption of the terpene lactones is dictated by their intermediate membrane permeability and they are not substrates of CYP3A4, UGT and P-gp at the gut \[120-121\]. Thus, augmentation of the oral absorption of these terpene lactones by piperine could plausibly be through the non-specific mechanism of enhancing the blood supply in the enteric vessel due to the local vasodilatory effect of piperine \[54\].

3.1.6 Other Bioenhancers with action as Piperine

Other herbal bioenhancers that have similar bioenhancing mechanisms of action like piperine (Genistein, Naringin, Sinomenine, \textit{Carum carvi}) might be expected to also augment oral absorption of phytoconstituents that are substrates of CYP3A4, UGT and P-gp. It will be worthwhile to subject this proposition to further research.

3.2 HMPs with Ginger (and Other Bioavailability Improvement Approaches)

3.2.1 \textit{Andrographis paniculata}

\textit{Andrographis paniculata} belongs to the family Acanthaceae and is an important medicinal plant widely used around the world \[122\]. The aerial part of this herb is most commonly used and has been reported to have a broad range of pharmacological effects including anticancer,
antihepatitis, antihyperglycemic, immunomodulatory, antibacterial, anti-inflammatory, antioxidant and antimalarial [123-125]. The phytochemicals extracted from this herb consist of diterpenoids, flavonoids, quinic acids, xanthones, andrographolide with its derivatives [126, 127]. The major bioactive compounds are the andrographolides which are diterpene lactones [125]. The chemical structures of some bioactive phytoconstituents isolated from *Andrographis paniculata* are presented in Fig. 5.

*Andrographis paniculata* extracts are standardized using andrographolide contents. Andrographolide has poor aqueous solubility and its oral bioavailability at therapeutic doses is very low [127-129]. The poor oral absorption of the product at the clinically useful dose necessitated reformulation of the extract to enhance its bioavailability. Several strategies have been used to improve the bioavailability of andrographolide from the herbal extract [130] and these include cyclodextrin complexation [131], preparation as herbosome [132,133], niosome formulation [134], nanoemulsion formulation [135], liquid and solid self-microemulsifying drug delivery systems [136], pH-sensitive nanoparticle delivery system [129], and solid lipid nanoparticle formulation [137].

In addition to these approaches, the incorporation of ginger, acting as a bioenhancer, significantly enhanced the bioavailability of *Andrographis paniculata* extract by up to 55%, through regulation of intestinal function to facilitate absorption [42,67,68]. Addition of piperine further increased the bioavailability to 70%, which suggests that the oral absorption...
can be bioenhanced through other mechanisms. Reports indicate that andrographolide is a substrate of P-gp [138], hence, inhibition of intestinal P-gp by piperine has the potential of potentiating the bioavailability of the compound [39]. Thus, the poor oral bioavailability of andrographolide is attributed to not only its poor aqueous solubility but also to its rapid gut biotransformation and efflux by P-gp [139].

3.2.2 Withania somnifera

*Withania somnifera* (family Solanaceae) also known as ashwagandha or Indian ginseng has been an important herb in the ancient system of Indian traditional medicine. The main parts of the plant used therapeutically are the roots. Results from animal studies and clinical trials support the use of this herb for treatment of anxiety, cognitive and neurological disorders, inflammation, hyperlipidemia and Parkinson's disease [140]. It has several other pharmacological activities including immunomodulatory, aphrodisiac and sedative properties [141]. The roots extracts of *Withania somnifera* consist mainly of steroidal lactones known as withanolides, which the medicinal properties of the herbal product are attributed to [142,143]. The major withanolides are withanolide A and D, and Withaferin A with their derivatives. Their chemical structures are presented in Fig. 6. Other biologically active chemical constituents are alkaloids of which withanine is the main constituent with other minor alkaloids such as somniferine, cuscohygrine, isopelletierine, anaferine andanahydrine [144].

![Chemical Structures of some bioactive phytoconstituents of *Withania somnifera*](image-url)
Steroidal lactones including withanolides generally have poor aqueous solubility and hence have bioavailability problems. Several approaches have been investigated aimed at increasing the solubility and bioavailability, and thus increase the pharmacological activity of this HMP. These include formulation of polymeric nanoparticles [145], phytosomes [146,147], and preparation of enteric coated dosage form of the herbal extract which protects the composition from hydrolysis in the acidic medium of the stomach, thus enhancing the absorption [148].

Incorporation of ginger into *Withania somnifera* extract increases its absorption by up to 64% [42]. This action is mediated via the established activity of ginger as a potent bioavailability enhancer which operates by regulation of intestinal function resulting in increased GIT drug absorption [42,67,68].

### 3.2.3 Picrorhiza kurroa

*Picrorhiza kurroa* (family scrophulariaceae), also commonly known as Kutki (Nepali language), is an important alpine herb that grows in limited regions and altitude and found especially in the Himalaya region. The roots and rhizomes of this plant are used in traditional medicine for treatment disorders of liver and upper respiratory tract, dyspepsia, diarrhea, and dysentery, among other ailments [149]. The HMP has also been shown to possess other pharmacological activities including antioxidant and anti-inflammatory [150,151]. The major bioactive constituents which its therapeutic effects are attributed to are irioi glycosides called picroside I and picroside II [152]. The chemical structures are presented in Fig. 7.

Like most irioi glycosides, the picrosides have poor intestinal permeability attributable to their high hydrophilic nature. Also, the glycosides undergo hydrolysis in the GIT and the released aglycones have poor bioavailability due to their limited aqueous solubility [153]. As a result of the poor bioavailability, this herbal product is recommended to be administered in higher quantities resulting in increased treatment cost [154]. Review of the literature shows that limited strategies have been developed to improve bioavailability of these biomolecules and these include a nano-encapsulation formulation of the plant extract [155]. Another study is an invention which reports on formulation of phytosomes of picroside II with phospholipid which significantly improves the bioavailability of picroside II [156].

Ginger extract was found to significantly increase the bioavailability of *Picrorhiza kurroa* product by as much as 56 % and this was increased further to 87% when piperine was added to the formulation [67,68]. Both are bioenhancers acting through different mechanisms [42].

#### 3.2.4 Tinospora cordifolia

*Tinospora cordifolia* (family Menispermaceae) grows throughout tropical Asia and its extracts have a broad range of pharmacological activities notable of which are anti-diabetic, anti-spasmodic, anti-inflammatory, anti-oxidant, anti-malarial, hepatoprotective, immunomodulatory and anti-neoplastic activities [157]. A variety of phytoconstituents isolated from the root, stem and whole plant have been identified to belong to different chemical classes, and the major group of compounds considered as the bioactive constituents are protoberberine alkaloids (egberberine, tembetarine, isocolumbin); diterpenoid lactones (eg furanolactone, tinosporon, tinosporide); steroids (eg β – sitosterol, δ-sitosterol,ecdysterone, giloinsterol) and glycosides (egcordifolioside, cordioside, tinoscirside, syringin) [157,158]. The chemical structures of some of these bioactive constituents are shown in Fig. 7.

It is apparent from the chemical structures of the various bioactive constituents of *T. cordifolia* that they have different degrees of hydrophilicity or lipophilicity. For example, steroids are lipophilic and generally have poor aqueous solubility while glycosides are hydrophilic and are associated with poor intestinal permeability. This entails that formulation modalities which can improve aqueous solubility and/or GIT permeability have the potential of enhancing the bioavailability of some constituents of this HMP. Few studies are reported on the bioavailability improvement of *T. cordifolia* extract. Using an everted gut model, when compared to control, about a 4-fold enhancement in permeability coefficient of *T. cordifolia* extract was obtained with nanoemulsion formulation of this HMP [159]. The authors concluded that the nanoemulsion formulation will result in enhancement of therapeutic efficacy through improved permeation of the active constituents across the GIT [159]. In another study, a significant enhancement of bioavailability of *T. cordifolia* product was observed when *Carum carvi* extracts was incorporated into the product [62]. *Carum carvi* extract has been reported to...
enhance the bioavailability of several synthetic and other herbal drugs and this bioavailability enhancing activity was found to be consistent from 5 to 100 mg/kg body weight irrespective of the amount of the drug(s) present in the formulation [62]. The mode of bioavailability enhancement action is thought to be by inhibition of P-gp mediated efflux of the absorbed compounds back into the GIT [38,40] since some constituents of T. cordifolia extract are substrates of P-gp [159].

Ginger extract was found to significantly increase the bioavailability of T. cordifolia product by up to 67% and this was increased further to 112% when piperine was added to the formulation [67, 68]. As earlier stated, ginger has a strong effect on GIT mucous membrane leading to regulation of intestinal function to facilitate absorption [42]. Piperine, being a P-gp inhibitor just like Carum carvi extract [38,39] could have potentiated the bioavailability by inhibition of P-gp efflux of T. cordifolia constituents.

Fig. 7. Chemical Structures of bioactive phytoconstituents of Picrorhiza kurroa and Tinospora cordifolia
4. CONCLUSION

Phytotherapy has been playing an important role in pharmacotherapy. However, there are numerous reports of poor bioavailability resulting in reduced in vivo activities of several medicinal plant extracts and phytoconstituents [34-36]. Improving the bioavailability of these HMP will go a long way in the optimisation of efficacies of the products. Extensive research work has been focused on the enhancement of oral bioavailability of the poorly absorbed orthodox medicines but this review has shown that HMPs are receiving relatively poor attention in this regard. The present review highlighted different strategies that can be employed to improve the bioavailability of HMPs with emphasis on the utility of bioenhancers derived from herbs.

It was found expedient to identify the bioactive phytoconstituents of the HMPs such that information on their physicochemical properties, metabolic fate and factors that impact on their gastrointestinal absorption were examined to serve as guide for application in the bioavailability enhancement of other HMPs with poor bioavailability of their active constituents. It is essential to understand the reason behind the poor bioavailability of bioactive moieties before selecting an appropriate technique or bioenhancer. The benefits of incorporation of suitable bioenhancers to drug products with poor bioavailability cannot be over-emphasized since this is associated with a reduction of dosage, drug toxicity and cost of the whole treatment.

Thus, there is a need for more research endeavours on a combination of HMPs with suitable bioenhancers since this has the potential of not only enhancing efficacy but also reducing drug treatment cost.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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