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Technology for improving the bioavailability of small molecules extracted from traditional Chinese medicines

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Evidence that small molecules extracted from traditional Chinese medicines (TCMs) have beneficial effects on health is increasingly being reported in the scientific literature and these compounds are now widely recognized as potential therapeutic drugs. There have been several detailed studies of the absorption, distribution, metabolism and excretion of these compounds in rats and humans. However, some active components have low bioavailability owing to their unsuitable physicochemical and biopharmaceutical characteristics, resulting in differences *in vivo*. The main problem in using natural products as a source of pharmaceutical lead compounds is the need to improve the bioavailability of these compounds. This review presents and discusses the current methods used for improvement and their impact on the bioavailability of some new pharmaceutical lead compounds from TCMs.

Keywords: absorption, bioavailability, small molecule, traditional Chinese medicine

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1. Introduction

Traditional Chinese medicines (TCMs) consist of natural products from plants, animals and minerals that have been used in China for several thousand years. In most cases TCMs involve hundreds of different constituents, belonging to different compound classes with diverse chemical constitutions and physicochemical properties. A variety of carbohydrates, phenylpropanoids, flavonoids, terpenoids, volatile oils, saponins and alkaloids isolated from medicinal herbs have been studied.

Many aspects, such as physicochemical properties and chemical parameters, play a role in the bioactivity of the active molecules. These relate to the transport of the bioactive compound to its site of action, usually a receptor or other biomacromolecule at the cellular or subcellular level. The structural features of a compound can be related to its pharmacological properties, either qualitatively or quantitatively. The principles, concepts and numerical rules governing qualitative and quantitative relationships between structure and activity help to explain the pharmacological activity of a new compound, which is why it is important to evaluate the structure of a newly isolated plant compound.

After the bioactive molecular entity has been identified, detailed data on its solubility, partition coefficient and the electrolytic behavior can be determined. Solubility characteristics are closely related to drug absorption, and the degree of absorption determines drug action. Many bioactive plant constituents are weak acids and bases, and their degree of ionization when dissolved is of great importance to their bioactivity. As a rule, the ionic form is more water-soluble.

These factors are important when bioactivity is related to drug distribution between the gastrointestinal tract and plasma, between kidney tubules and urine,

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and between plasma and other body compartments. Generally speaking, only the lipid-soluble and undissociated forms of a bioactive molecule will pass through membranes. However, at the site of action, bioactive compounds may generate their action by binding to a receptor on the cell membrane. Consequently, it is important not only to know which form of bioactivity is present in small molecules of TCMs, but also to know how much of that constituent is bioavailable. To quantify the amount that is actually absorbed, distributed to tissues, metabolized and eventually excreted, the term bioavailability was introduced. Bioavailability describes the concentration of a given compound or its metabolite at the target organ; however, no single definition exists that accurately takes into account the multifactorial nature of the term. The US Food and Drug Administration defines bioavailability as 'the rate and extent to which the therapeutic moiety is absorbed and becomes available to the site of drug action'. Owing to difficulties in accessing organ sites *in vivo* in humans, attempts to use the term with quantitative precision or to calculate exact values in humans are challenging. As a consequence, the term 'absolute bioavailability' is often used by clinical pharmacologists to describe the exact amount of a compound that reaches the systemic circulation, calculated as the fraction of the area under the curve (AUC) after oral ingestion compared with the AUC after intravenous administration. The other term 'relative bioavailability' is commonly used to describe the bioavailability of a compound from one preparation compared with another. The 'classical', pharmacological definition of bioavailability covers several linked and integrated processes, specifically, liberation, absorption, distribution, metabolism and excretion. Here, the technology for improving the bioavailability of small molecules of TCMs according to many factors influencing their pharmacological actions is reviewed.

2. History of TCMs and bioavailability

Herbal medicine is an empirical healthcare system based on human experience dating back several thousand years [1]. Substances having curative effects are chemical components, including three groups of matter: minerals, small molecular organic compounds (such as naphthas, alkaloids, flavones and saponins) and biomacromolecules (such as peptides, albumin, glycopeptides and polysaccharides) [2], and here small molecular organic compounds are discussed.

Prescriptions are the main formulations of TCMs, which are quantified and formulated according to the principles of the relevant scientific authorities based on attempts to choose the most suitable dose of medicine. Compound prescriptions are complex systems and come from long-term medical practice with a scientific meaning and clinical value [2]. The law of compatibility is the key element of complex prescription of TCMs.

A series of experiments designed by Yang *et al.* demonstrated that in some compound recipes one certain component could affect the bioavailability of the other components. In one experiment [3], they compared the effect of *Radix Paeoniae Rubra* (control group) and a combination of *Cortex Cinnamomi* and *Radix Paeoniae Rubra* (treated group) on the plasma concentration of paeoniflorin in mice. *Cortex Cinnamomi* was able to increase the plasma concentration of paeoniflorin in a complex prescription of *Cortex Cinnamomi* and *Radix Paeoniae Rubra*. The plasma concentration of paeoniflorin for the control group was 42.28 ± 4.43 ng/μl, whereas that of the treated group was 54.28 ± 5.81 ng/μl. There was a significant difference between the two groups. Another trial [4] involved studying the influence of Chinese herbs on the bioavailability of paeoniflorin and the mechanism of action. Chinese herbs (pepper fruit, evodia fruit, cassia bark, fennel fruit and prickly-ash peel) were separately used in combination with paeoniflorin for administration by gavage to mouse. The relative bioavailability of paeoniflorin was 137.22% for pepper fruit, 123.62% for evodia fruit, 108.39% for cassia bark, 226.02% for fennel fruit and 116.73% for prickly-ash peel. The Chinese herbs used in this experiment in combination with *Radix Paeoniae Rubra* were able to enhance the bioavailability of paeoniflorin, which illustrated the scientific importance of the recipe combination of Chinese herbs for activating blood circulation and inner-warming from a pharmacodynamic point of view.

In addition, other studies by Yang [5,6] proved that *Cortex Cinnamomi Cassiae* or *Piper nigrum* combined with *Radix Angelicae Sinensis* increased the relative bioavailability of ferulic acid, which is the main component of *Radix Angelicae Sinensis*.

These tests prove that the existing prescriptions are not only efficient as far as treatment is concerned, but are also based on scientific theory. The compatibility of certain components can increase the absorption of other components, and thus improve the overall bioavailability.

3. Modern research of TCM biopharmaceutical

TCMs have been used to prevent and cure disease in China for centuries, and they have become more popular around the world during the last decade. However, the problems of poor bioavailability and lack of fundamental research have restricted their further development and acceptance internationally. Increased knowledge and a better understanding of TCMs have become necessary and a matter of urgency. Modernization of TCMs means examination of herbal medicines with modern technology, modern academic thinking and scientific attitudes [2].

The importance of TCMs together with their bioactive ingredients is increasingly recognized nowadays owing to their effectiveness and safety. However, many TCMs and bioactive ingredients are manufactured under primitive conditions in China, and modernization is necessary. To improve their performance, it is necessary to revise the dosage forms for TCMs and bioactive ingredients using modern advanced technology.

As reported, to prolong the duration of breviscapine in the circulation, reduce the frequency of injection administration and, subsequently, improve patient compliance, multivesicular

liposomes (MVL, namely DepoFoam) [7] have been used as a sustained delivery system for breviscapine. Drug release from bre-MVLs (triolein/tricaprylin) *in vitro* took place over a long period of 5 – 6 days, whereas the bre-TLs (traditional liposomes containing breviscapine) released 80% within 4 h, so MVL could be used successfully as a sustained delivery system for breviscapine.

Another study showed that silymarin proliposomes prepared by film deposition on carriers had a high encapsulation efficiency of > 90%, with an average particle size of ~ 238.8 nm and very good stability [8]. The high bioavailability of silymarin proliposomes could be obtained by oral administration.

The particle size of TCMs is an important physical property that affects several pharmaceutical characteristics, such as dissolution, chemical stability and bioavailability of solid dosage forms [9]. It has been found that nanotechnology and nanomaterials can play a significant role in improving the utilization of herbs, controlling release systems, and enhancing the targeting ability [10].

In one trial, *Radix salvia miltiorrhiza* nanoparticles ~ 133.5 nm in size were prepared using a high-speed centrifugal sheering pulverizer. The subsequent *in vitro* release study showed that *R. salvia miltiorrhiza* microcapsules showed controlled drug release [11].

Another trial also testified to the conclusion: triptolide-loaded poly(DL-lactic acid) nanoparticles, with a mean size of ~ 150 nm and polydispersity index of 0.088, which were prepared by the modified spontaneous emulsification solvent diffusion method (modified-SESD method) [12]. The *in vitro* release profile of triptolide from these nanoparticles showed a typical biphasic release profile, namely an initial burst release and subsequent sustained release. In this case, the particle size played a key role in the drug release.

There are other dosage forms that can increase bioavailability, such as: solid dispersions, which can greatly enhance dissolution; microspheres, which have good prolonged release *in vivo*; phosphatidylcholine complexes, which can increase the rate of absorption; and microemulsions, which can also enhance absorption [13]. Other modern technological approaches have been used or will need to be applied to TCMs to enhance their bioavailability.

4. Bioavailability study of small molecules extracted from TCMs

Fifteen small molecules by categories and modern technology successfully used to enhance bioavailability are listed in **Table 1**.

4.1 Saponins

Saponins, generally known for their predominant surface-active properties, are a large group of glycosides widely distributed in plants. They are structurally diverse molecules that can be chemically referred to steroidal saponins and triterpenoid saponins based on the nature of their aglycone skeleton. The structure of saponins always contains a non-polar mother nucleus coupled with one or more monosaccharide moieties.

Owing to the numerous pharmacological actions of saponins, they are believed to be the main functional components of TCMs that have been widely used for centuries. Of these, ginsenosides are generally divided into 20*(S)*-protopanaxadiol groups and 20*(S)*-protopanaxatrial groups (represented by ginsenoside Rb1, Rg1, respectively), saikosaponins (such as saikosaponin a, b, c, d) and glycyrrhizins, as well as ophiopogonin (mainly involving steroidal saponins), which have received a great deal of attention.

The pharmacokinetics of ginsenoside Rb1 has been investigated by thin-layer chromatography. The conclusion obtained is that little Rb1 is absorbed from the digestive tract of rats and, simultaneously, it can be easily destroyed in the stomach [14]. Odani *et al.* also studied ginsenoside Rg1, showing that 80% of a dose of Rg1 was still present in the gastrointestinal tract 2.5 h after oral administration to rats and the amount of Rg1 absorbed was in the range of 1.9 – 20.0% of the oral dose [15]. Other reports in the literature have shown that the bioavailability of Rb1 was barely 0.1%, whereas that of Rg1 was 1.9% after oral administration to rats [16]. Xu *et al.* developed and applied HPLC methods to study the pharmacokinetics of them, with the result that the oral bioavailability was 4.35% for Rb1 and 18.4% for Rg1 [17].

In addition, Han *et al.* used the Caco-2 cells and rat models to evaluate the degradation of Rb1 and Rg1 in *Panax notoginseng* saponins in the gastrointestinal lumen, and to study the transport mechanism of *P. notoginseng* saponins across the intestinal mucosa as well as the barrier function of the stomach, intestine and liver involved in the absorption process. Moreover, they identified several potential reasons for the low absorption and bioavailability of ginsenosides [18]. First, both Rg1 and Rb1 were extremely unstable in an acidic environment, and > 90% of Rb1 and 80% of Rg1 were destroyed after being incubated for 2 h in simulated gastric fluid [19]. Second, enzymes or bacteria in the gastrointestinal tract metabolized the drugs after oral administration. Despite the different metabolic pathways of ginsenoside Rg1 in the human and rat intestinal tracts, the final metabolite was 20*(S)*-protopanaxatrial. Moreover, ginsenoside F1 and Rh1, as intermediate metabolites of Rg1 in the human and rat intestine, were isomers. Ginsenoside Rb1 undergoes identical conversion in the human and rat intestine, being converted to ginsenoside Rd and ultimately to ginsenoside F2-20-*O*-β-glucopyranosyl-20*(S)*-protopanaxaial [20]. Last but not the least, the cause was their poor absorption in the intestine. The apparent permeability coefficients of Rg1 and Rb1 were extremely low (1×10^{-7} – 1×10^{-8} cm/s) [19]. The hydrophilicity of glycosyls in ginsenosides together with their greater molecular mass (Rg1 801, Rb1 1109.3) was unfavorable to the drug transport through the cell membranes.

Some researchers have indicated that the transport across Caco-2 cell monolayer for *P. notoginseng* saponins (including Rb1 and Rg1) is a simple passive diffusion process [19]. No

Table 1. Summary of small molecules from TCMs by categories and modern technology used to enhance bioavailability.

Small molecules	Categories	Plant	Modern technology	Ref.
Paeoniflorin	Monoterpenes	*Radix Paeoniae Rubra*	The recipe combination	[3,4]
Ginsenoside Rb1 and Rg1	Saponins	*Radix Notoginseng*	Microemulsions	[23]
Breviscapine	Flavones	*Gerbera jamesonii Bolus*	Multivesicular liposomes	[7]
Silymarin	Flavonoids	*Silybum marianum* (L.) *Gaertn*	Proliposomes	[8]
Quercetin	Flavonols	*Flos Sophorae Iimmaturus*	Solid lipid nanoparticles	[30]
Rutin	Flavonols	*Flos Sophorae Iimmaturus*	Microcapsules	[33]
Hesperetin	Flavanones	*Fructus Ponciri Trifoliatae*	β-cyclodextrin complexation	[34]
Naringenin	Flavanones	*Citrus Maxima (burm.f.) Merr*	β-cyclodextrin complexation	[34]
Tanshinol	Phenolic acids	*Salvia miltiorrhiza Bunge*	P-gp inhibitor	[47]
Berberine	Alkaloids	*Cortex Phellodendri Amurensis*	P-gp inhibitor	[51]
Camptothecin	Alkaloids	*Camptotheca acuminate Decne*	Prodrugs Micelles Nanoemulsion	[55] [56] [57]
Myrtle oil	Essential oil	*Rhodomyrtus tomentosa (Ait.) Hassk*	Enteric-coated capsules	[64]
Schisandrin C	Lignans	*Fructus Schisandrae Chinensis*	Drug–drug interactionsP-gp inhibitor	[81]
Ginkgolide B	Lactone	*Ginkgo biloba* L	Sustained-release preparation	[86]
Triptolide	Lactones	*Radix Tripterygii Wilfordii*	Nanoparticles	[12]

efflux transporters in Caco-2 cells, such as P-gp and MRP (multi-drug resistance-associated protein), had any effect on it. However, others [21] have shown that, besides the passive diffusion mechanism, facilitated diffusion and active transport may also play a role in the transport process. Feng *et al.* compared the absorption-promoting effect of different types of absorption enhancer and different concentrations of sodium dodecyl sulfate, carbomer and borneol. Statistical analysis showed that carbomer and borneol significantly enhanced the intestinal absorption rate of Rg1 and Rb1, whereas sodium lauryl sulfate had no effect. Moreover, the effect of borneol was greater than that of carbomer [21]. The absorption-promoting mechanism of carbomer and borneol showed that the tight junctions were closely involved in the absorption of water-soluble saponins [21]. Other researchers have examined the bioavailability by development of other formulations of saponins. For example, Wu *et al.* developed a *P. notoginseng* saponin intranasal preparation, and the bioavailability of Rg1 was equivalent to that of intravenous injection [22]. Han *et al.* also selected soybean phospholipids/ethanol as a surfactant or co-surfactant, together with *P. notoginseng* saponin solution and various kinds of oil to prepare 11 kinds of water-in-oil microemulsion. They found that most of the microemulsions enhanced the intestinal absorption of Rb1 significantly by comparing the permeability coefficient values of Rb1 and, moreover, the enhanced intestinal absorption of Rb1 was attributed to its improvement of membrane fluidity owing to the presence of the surfactant/co-surfactant and oil in water-in-oil microemulsions [23]. According to a study concerning the impact of menthol on the apparent bioavailability of an analgesic composition of *Bupleurum fruticescens* L., menthol enhanced the absorption of the analgesic ingredient that had been confirmed to be saponin, and the mechanism may have no relation with the pharmacological action of menthol. Ching *et al.* discovered that honey could promote the conversion of glycyrrhizin to glycyrhetinix and, furthermore, could inhibit glycyrhetinix metabolism and promote the absorption of glycyrhetinix, thereby enhancing the role of licorice [24].

Nowadays, investigation of the transport mechanism and metabolic pathway of saponins has shown that factors of the gastrointestinal tract are the principal barrier to drug adsorption, whereas enzymes or bacteria in the gastrointestinal tract play an important role in the case of saponins. The combination of polar and non-polar structural elements in the molecules is also responsible for their adsorption behavior *in vivo*. Consequently, the oral bioavailability of saponins is extremely low, and thus we should consider these effects with a view to the clinical application of saponins. Research directed at improving the bioavailability has two important aspects, one is to change the route of administration and avoid metabolism by enzymes or bacteria in the gastrointestinal tract, whereas the other is the development of formulations involving the addition of different types of absorption enhancer. Later research has involved many kinds of new dosage forms for

the preparation of saponins, such as microemulsions, and phytosomes of saponins. The use of correlative absorption enhancers has been confirmed to be able to improve the bioavailability of saponins to a certain extent and, therefore, the development of those should be a topic for future research.

4.2 Flavonoids

Flavonoids belong to a large group of polyphenolic compounds that are widely distributed in herbal medicines and foods of plant origin. More than 5000 different flavonoids had been described by 1990. According to a common diphenylpropane structure (C6-C3-C6) and variations in the C-ring, flavonoids can be subdivided further into six major subclasses consisting of flavones (e.g., apigenin, luteolin), flavonols (e.g., quercetin, myricetin), flavanones (e.g., naringenin, hesperidin), catechins or flavanols (e.g., epicatechin, gallocatechin), anthocyanidins (e.g., cyanidin, pelargonidin) and isoflavones (e.g., genistein, daidzein) [25]. Most of the flavonoids present in TCMs are attached to sugars (glycosides), although occasionally they are found as aglycones. These compounds have been reported to be strong antioxidants, inhibiting the growth of cancerous cells and inflammation as well as acting as vasoprotectors, and having anti-obesity effects [26].

The biological activities *in vivo* are dependent on the absorption and bioavailability of constituents of the TCMs. There have been several studies that have investigated the absorption and bioavailability of flavonoid compounds [27]. Hollman *et al.* [28] conducted a study to examine the extent of absorption of quercetin glucosides, quercetin rutinoside and pure quercetin aglycone. They based their findings on indirect evidence and proposed that flavonoid glycosides could be absorbed intact in the small intestine, using the sodium-dependent glucose transporter. Margreet *et al.* concluded that quercetin glucosides are rapidly absorbed in humans, irrespective of the position of the glucose moiety. Conversion of quercetin glycosides into glucosides is a promising strategy to enhance the bioavailability of quercetin [29]. Further studies [30] in healthy individuals have reported similar results and suggested that the glycoside moiety actually enhances absorption. The present study is to design quercetin-loaded solid lipid nanoparticles (QT-SLNs) and clarify the absorption mechanism of QT-SLNs. Determination of the relative bioavailability of QT-SLNs to quercetin suspension was 571.4% [31]. The results indicate that using solid lipid nanoparticles as an oral delivery carrier for poorly water-soluble drugs is feasible.

Recently, researchers have explored the bioavailability of isoflavones and tried to isolate a bacterium capable of transforming puerarin to daidzein, and examined the production of equol from puerarin using a mixed culture of two isolated bacteria [32]. Genistein has already been shown to inhibit P-gp activity and the sulfation of *p*-nitrophenol, and both genistein and daidzein are capable of inhibiting glucuronidation. Moreover, genistein was found to be capable of inhibiting CYP1A- and CYP2E1-dependent metabolism in mouse liver microsomes [32]. Xiao *et al.* [33] prepared rutin–alginate–chitosan microcapsules by complex-coacervation to increase the absorption.

The extent of absorption and bioavailability of flavonoids has long been known to be affected by membrane transporters, colonic microflora and metabolic enzymes. Due to the low water solubility, a study was undertaken to improve the solubility and dissolution properties of hesperetin and naringenin by β-cyclodextrin complexation [34]. There is enormous interest in such flavonoids as prototypes for studies using suitable drug delivery vehicles (e.g., cyclodextrins) capable of ensuring increased hydrosolubility, and consequently improved bioavailability [35]. In addition to the functions of targeting and slow-release, producing the TCMs as nanoparticles can also reach the choice of formulations, promote the drugs through the biological barriers and increase the bioavailability of drugs [36].

4.3 Organic acids

Organic acids, carboxyl compounds (-COOH), are distributed extensively in the leaves and roots of herbal medicines, in particular in fruits, such as *Fructus mume* and *Fructus schisandra*. They can be chemically divided into aliphatic and aromatic acids. The common aliphatic acids in plants are monacid, binary and multi-carboxylic acids such as tartaric acid, malic acid, citrate and ascorbic acid, whereas the most common aromatic organic acids are benzoyl acid, salicylic acid and caffeic acid. Apart from a few in the free state, they are generally combined with potassium, sodium and calcium as salts, and some are even combined with alkaloids.

It is generally believed that no special biological activity is shown by aliphatic organic acids, whereas the derivatives of caffeic acid have a certain degree of biological activity. For example, chlorogenic acid is a hydroxycinnamic acid that is a multi-hydroxy acid, and it is an ester of caffeic acid with quinic acid. *Salvia miltiorrhiza Bunge* has been used widely in TCMs for the treatment of coronary heart disease. Two types of major bioactive component include water-soluble phenolic acids and lipophilic diterpenoid quinines, and Li has systematically separated and identified 15 phenolic acids, including polyphenolic acids (such as various salvianolic acids) and related compounds [37].

Lafay *et al.* has examined the absorption of chlorogenic acid using biliary translocase [38], while a study using a Caco-2 cell model shows that the absorption may also take place by means of passive transport [39]. Chlorogenic acid is taken up by the intestine, whereas the degree of hydrolysis into caffeic acid is barely 1% [40]. The intestinal absorption and excretion was described further by Olthof et al., who found that about one-third of oral chlorogenic acid entered into the blood circulation through the intestinal mucosa, whereas the remaining two-thirds of chlorogenic acid entered the cecum and colon [41]. Chlorogenic acid can undergo a wide range of microbial metabolic conversions to various metabolites besides free caffeic acid and quinic acid [42]. The

oral bioavailability of chlorogenic acid is largely dependent on metabolism by intestinal flora metabolism [43], and so the low bioavailability can be attributed to extensive metabolism in the intestine.

Although most phenolic acid compounds of *S. miltiorrhiza Bunge* displayed protrudent bioactivity for the treatment of angiocardiopathy, the low oral bioavailability markedly restricts their clinical application. Zhang *et al*. have evaluated the bioavailability of salvianolic acid B in restrained rats and found that the oral bioavailability was 0.02%, which is very different from the value of 2.3% obtained using an automated blood sampling system in stress-free rats [44]. In addition, they also found that > 60% of the dose of salvianolic acid B remained in the gastrointestinal tract 4 h after oral administration, which indicated the poor absorption of salvianolic acid B in the rat small intestine. A previous report using the microdialysis technique had shown that the concentration of unbound salvianolic acid B in bile was much higher than that in blood, suggesting that salvianolic acid B can easily be eliminated through the hepatic duct. A study of the absorption kinetics of salvianolic acid A in the rat small intestine [45] indicted that the intestinal absorption of salvianolic acid A was very low, on average only 20.5%. The reason for this was mainly attributed to the poor penetration of salvianolic acid A following dissociation under alkaline conditions in the gastrointestinal tract. Furthermore, the absorption mechanism of alvianolic acid A was by means of passive diffusion.

Owing to the absorption mechanism and metabolic pathway of phenolic acid compounds of *S. miltiorrhiza Bunge* being very dissimilar, methods for improvement of the oral bioavailability are complicated. Song *et al*. compared the pharmacokinetic parameters of interrelated active ingredients of monomer and hydrophilic extracts, and found that some components in the hydrophilic extract reduced the absorption of protocatechualdehyde while they enhanced the absorption of the salvianolic acid B and reduced its elimination rate [46]. The study of the pharmacokinetic interaction between tanshinones and polyphenolic extracts of *S. miltiorrhiza Bunge* by Guo *et al*. [47] indicated that the elimination rate of salvianolic acid B and tanshinone IIA both decreased when given as an emulsion, possibly owing to uniform liver metabolism and biliary excretion [48]. According to this study of the pharmacokinetic effects of borneol on *S. miltiorrhiza Bunge* in compound preparations, it appeared that borneol can significantly increase the pharmacokinetic parameters of $t1/2\alpha$, $t1/2\beta$, $k\alpha$, AUC $(0 - \infty)$ of tanshinol, which pointed to the use of borneol as an auxiliary herb to increase the bioavailability and enhance the permeability of tanshinol, but reduce the rate of metabolism. In addition, some researchers have used the Caco-2 cell model to examine the intestinal absorption of tanshinol. The results obtained show that the transport of tanshinol may be via active transport mediated by P-gp transporter, suggesting that a specific inhibitor of P-gp, such as verapamil, could suppress the efflux role of P-gp, and consequently improve the intestinal absorption of tanshinol. According to a current investigation concerning the poor absorption of interrelated organic acids in the gastrointestinal tract, the potential reasons are extensive metabolism in the gastrointestinal tract, the effect of efflux transporters, together with poor intestinal permeability caused by drug dissociation in the small intestine.

4.4 Alkaloids

Alkaloids are organic nitrogenous bases found mainly in plants, but also to a lesser extent in microorganisms and animals. One or more nitrogen atoms are present, typically as primary, secondary, or tertiary amines, and this usually makes alkaloids basic. According to the nature of the nitrogen-containing structure, alkaloids are often classified as pyrrolidines, piperidines, quinolines, isoquinolines, and indoles. Alkaloids contained in the TCMs have very different structures, and undergo complex metabolic processes and show a range of therapeutic effects. Berberine, which is used to treat diarrhea, is an isoquinoline alkaloid found in plant genera Berberis and Coptis. Berberine chloride is the common form of berberine in many plants [49]. Recently, it has been found that berberine has many other biological activities, including beneficial effects on ocular trachoma infections, cardiovascular effects, and anti-inflammatory effects.

Berberine, however, has a low bioavailability, which limits its applications in a wide range. Poor solubility is one reason for decreased absorption in the gastrointestinal tract [50]. Drug molecules have to be dissolved in fluid before absorption and high solubility leads to excellent bioavailability of drug molecules. Therefore, enhancing the solubility of berberine by using technologies such as solid dispersion may be an important way to improve its biological availability. Extended-release oral dosage forms might be another way to improve the bioavailability of berberine. P-gp could also affect the absorption of berberine in the gastrointestinal tract. Pan [51] used the P-gp inhibitors cyclosporin A, verapamil and the monoclonal antibody C219 in a series of *in vivo* and *in vitro* models of intestinal absorption to determine the role of P-gp in berberine absorption. Berberine absorption was improved sixfold by P-gp inhibitors in a rat recirculating perfusion model. In a rat-everted intestinal sac model, berberine serosal-to-mucosal transport was significantly reduced by cyclosporin A. The rate of serosal-to-mucosal transport across the rat ileum was threefold higher than in the reverse direction and was significantly reduced by cyclosporine A in an Ussing-type chamber. P-gp appears to result in poor absorption of berberine through the gut wall, which suggests that P-gp inhibitors could be of therapeutic value by improving its bioavailability [51].

Matrine is an alkaloid isolated from the root of *Sophora subprostrata* (Leguminosae) that has been used in Chinese medicine for the treatment of inflammation. Matrine can also be used as an analgesic and this has been investigated using the hot plate test [52]. At present, matrine injections are used to treat hepatitis patients in China. Zhang *et al*. carried out a pharmacokinetic study of matrine, oxymatrine and

oxysophocarpine in rat plasma after simultaneous oral administration. The matrine, oxymatrine and oxysophocarpine concentration–time profiles fitted a two-compartment pharmacokinetic model. Oxysophocarpine was rapidly absorbed with a T_{max} of 1.58 h and was rapidly eliminated. However, the pharmacokinetic behavior for matrine was different. Matrine was absorbed with a T_{max} of 2.08 h, and then slowly eliminated while its plasma concentration remained very high. There were several reasons for the differences in the pharmacokinetic behavior of matrine and oxymatrine. One reason is that the other constituents in the *Sophora flavescens* extract had an influence on the transformation reaction, and on the absorption, distribution, metabolism and excretion of the two agents [53].

Camptothecin, an extract from the Chinese tree *Camptotheca acuminata Decne.*, is one of the most important drugs used to treat lung, ovarian, breast, pancreas and stomach cancer by targeting intracellular topoisomerase I, a nuclear enzyme that reduces the torsional stress of supercoiled DNA [54]. In addition, camptothecin has many other biological activities, such as antiviral and immunosuppressant effects. However, the extreme insolubility of camptothecin has seriously restricted its clinical applications. To resolve this issue, several strategies such as modification of the transport form have been used by many researchers. Prodrugs are temporary chemical modifications of the parent drug that are devised to enhance its aqueous solubility and biodistribution while keeping its inherent pharmacological properties intact. Conover *et al.* used polyethylene glycol-conjugated camptothecin-20-*O*-glycinate, PEG-β-camptothecin as a new water-soluble transport form. He found that PEG-β-camptothecin in saline provided more available labeled camptothecin in the circulation than unconjugated camptothecin dissolved in intralipid [55]. To increase the solubility and cytotoxicity of camptothecin, mixed micelles made of pluronic P105 and D-α-tocopheryl polyethylene-glycol-1000 succinate were prepared by Gao *et al.* [56]. Han *et al.* [57] developed a new oil-in-water nanoemulsion for 10-methoxy-9-nitro camptothecin and enhanced its solubility, stability and anticancer activity.

The alkaloid strychnine is isolated from *Strychnos ignatii Berg.* and is highly toxic. Strychnine has inhibitory effects against cell growth of various tumor cell lines [58,59]. Ma *et al.* demonstrated that the key mechanism of the intestinal absorption of strychnine was passive diffusion, whereas it was partially ATP-dependent for icajine [60].

Many strategies have been used to improve the therapeutic effect of alkaloids with poor bioavailability. P-gp inhibitors can reduce the efflux of alkaloids out from cells [51]. Several techniques have been used, such as solid dispersions, extended-release oral dosage forms, PEG-conjugation and nanoemulsions. In addition, the interaction of alkaloids may change their bioavailability.

4.5 Volatile oils (essential oils)

Volatile or essential oils are usually obtained from appropriate plant material by steam distillation, and other techniques, such as solvent extraction, may be used if certain components are unstable at higher temperatures. These oils, which typically contain mixture of low boiling point components, are widely used in flavoring, perfumery and aromatherapy. Some oils have useful therapeutic effects, especially those from TCMs, such as cinnamon bark, aniseed and nutmeg [61].

Myrtle oil is extracted from the leaves of myrtle. It has antiseptic, antibacterial, anti-hyperglycemic, antioxidant and analgesic effects. Sepici *et al.* [62] have investigated the oral hypoglycemic activity of single- or multiple-dose administrations of myrtle oil in normal and alloxan-diabetic rabbits. Myrtle oil showed good hypoglycemic activity in diabetic animals 4 h after administration. The reduction in the blood glucose level may be because of the reversible inhibition of α-glucosidases present in the brush-border of the mucosa of the small intestine [63]. Co-administration with other drugs may affect the therapeutic activities and bioavailability of myrtle oil. For example, the combination of myrtle and 1,8-cineol has shown clinical efficacy against acute bronchitis and sunibronchitis. Also, standardized myrtle co-administered with oxytetracycline is an effective treatment of sinusitis. In addition, differences in dosage form may also alter the biological effects of myrtle oil. Enteric-coated capsules containing myrtle oil showed different absorption properties in crushed and uncrushed capsules [64]. This indicates that myrtle oil can be used to treat a variety of diseases and it has different biological effects in different preparations.

Zhang *et al.* [65] investigated the regulative effects of the essential oil extracted from *Atractylodes lancea* on delayed gastric emptying in stress-induced rats. The results showed that the essential oil had no effect on normal gastric emptying function, but significantly regulated abnormal gastric emptying. To display all the functions of preparations, the volatile oils must be well retained. However, during production and storage, the volatile ingredients always degrade very quickly, which leads to a reduced therapeutic effect and adversely affects the appearance of the preparations. To prevent the loss of essential oils, β-cyclodextrin inclusion compounds were prepared [66]. These inclusion compounds can be used in many dosage forms to improve the bioavailability of essential oils and allow as wide a range of applications as possible.

Cinnamon, a plant of the Lauraceae family, has been used in Chinese traditional medicines for centuries. Its essential oil has many therapeutic effects and has been used to treat dyspepsia, gastritis, blood circulation disturbances and inflammatory conditions [67]. The extraction method has a significant influence on the bioavailability of essential oils. Wang *et al.* [68] investigated the xanthine oxidase inhibitory activity and anti-hyperuricemia effect in mice of essential oils from the leaves of *Cinnamomum osmophloeum*. The results indicated that the essential oils showed the strongest xanthine oxidase inhibitory activity. However, ethanol and hot water extracts showed no inhibitory effects, which indicated that the extraction process may have an apparent impact on the biological activities of essential oils.

Vian *et al.* [69] developed a new process for the extraction of essential oils. Microwave hydrodiffusion and gravity is a combination of the use of microwaves for hydrodiffusion of essential oils from the inside to the exterior of biological material and the earth's gravity to collect and separate the components. Compared with a conventional technique, hydrodistillation, for the extraction of essential oil from two aromatic herbs spearmint (*Mentha spicata* L.) and pennyroyal (*Mentha pulegium* L.), the essential oils extracted by microwave hydrodiffusion and gravity for 15 min were quantitatively (yield) and qualitatively (aromatic profile) similar to those obtained by conventional hydrodistillation for 90 min.

As we mentioned above, the biological effects and bioavailability of essential oils are linked to many aspects. Co-administration with other compounds has a significant impact on the activities of essential oils. The dosage form also affects their usefulness. Several new techniques have been used to improve the biological activities and bioavailability, such as soft shell capsule dosage forms, and β-cyclodextrin inclusion compounds [66]. In addition, the extraction process has a great impact on the properties of essential oils and, therefore, affects their biological activities to a certain degree. However, further investigations on the bioavailability are required, which will make possible the wider application of essential oils.

4.6 Lignans

Lignans are very widely distributed and found in cereals and in berries and, in much larger quantities, in flaxseed. The compounds are derived from condensation of phenylpropane or phenylpropanoid units and are always combined with polysaccharides. The major lignans are syringiresinol, pinoresinol, lariciresinol, isolariciresinol, matairesinol and secoisolariciresinol, usually found as glucosides and diglucosides [70]. Most lignans have structural similarities to the human female hormone, 17β-estradiol, and other steroid hormones and can bind to estrogen receptors in many tissues and exert weak estrogenic activity [71]. There is evidence that they have potential health benefits in humans, particularly against hormone-dependent diseases such as breast and prostate cancer and osteoporosis.

Despite the structural diversity and different sources of plant lignans, they undergo conversion to enterodiol and enterolactone by human gut microbiota [72,73]. These reactions have been shown to occur following *in vitro* incubation of lignans with human feces [74]. Antibiotic treatment of human subjects reduces the excretion of lignan metabolites, providing some evidence of the importance of bacterial flora [75]. Bowey *et al.* have investigated the metabolism of lignans in human flora-associated rats, in order to provide unequivocal evidence for the role of gut microflora in the absorption and metabolism of the constituents. Furthermore, the study also investigated whether the metabolic characteristics (high equol-producing and low equol-producing status) of human intestinal flora can be transferred to germ-free rats [76].

Chemical investigation of *Fructus Schisandrae Chinensis* revealed the presence of eight dibenzocyclooctadiene lignans, which have been identified and quantitated. These lignans are low-molecular-mass compounds and are believed to be responsible for the reported biological effects [77]. Gomisin A was found to reverse P-gp-mediated multi-drug resistance in cancer cells without affecting the expression of P-gp [78]. In another study, lignans (gomisin A, N and schisandrin C) were shown to inhibit strongly the CYP3A4 enzyme [79], indicating the possibility of drug–drug interactions in the presence of other components. In addition, some researchers have used the Caco-2 cell model to examine the intestinal absorption of three lignans (gomisin A, gomisin N and schisandrin C), a mixture of lignans and Schisandra extract to understand better the bioavailability, transport mechanism and drug–drug interactions of these dietary supplements. The results showed that gomisin A was transported predominantly by means of passive diffusion in the isolated form, and the transport of gomisin N was mediated by MRP (multi-drug resistance-associated protein) transporter, indicating that gomisin N may bind competitively to the MRP substrate site, and thus may act as an inhibitory substrate [80]. The results obtained from pharmacokinetic studies suggested that some ingredients in *Radix ginseng* and *Radix ophiopogonis* could increase the dissolution of schizandrin and other lignans when decocting, leading to a higher absorption of lignans in the decoction when using the same quantity of *Fructus Schisandrae Chinensis* [81].

The common use of TCMs has, however, been associated with some adverse effects, such as drug–drug interactions. Often these drug–drug interactions are reported, and are mediated by P-gp and MRP transporters. Such adverse reactions have caused serious concerns in recent years and a detailed evaluation of the bioavailability of native medicines has become necessary.

4.7 Lactones

Lactone compounds refer to one of numerous and widely distributed groups of substances with lactone rings found in herbs, such as ginkgolide, helenalin, ligustilide and triptolide. Over the last decade, substantial scientific evidence has accumulated that suggests that concentrated and partially purified lactones of herbs afford protection against some kinds of neural and vascular damage and are effective against cognitive deficits and other age-associated impairment. Ginkgolides are a unique group of diterpenes that exist naturally in the leaves of the Ginkgo biloba tree and include ginkgolides A, B and C [82]. In particular, ginkgolide B has been shown to protect against neural damage in a variety of circumstances. In addition, it has been shown to have beneficial effects on circulatory and inflammatory conditions [83].

Owing to the presence of lactone rings, these compounds are highly ionized at physiological pH or above. Recently, to increase the stability of the lactone ring, the lactone rings of ginkgolide A were converted into corresponding tetrahydrofuran moieties by means of DIBAL-H (diisobutyl aluminum hydride) reduction followed by deoxygenation of the formed

lactols [84]. Frequently, drug molecules with ionizable groups have only a narrow absorption window, and are absorbed only in that segment of the gastrointestinal tract where the unionized form constitutes a significant fraction of the drug molecules. In such cases, it is difficult to determine from *in vivo* studies whether the poor absorption of a drug is a result of ionization or poor intrinsic permeability of the uncharged drug [85].

Caco-2 cell monolayers and closed loop *in situ* experiments were performed to study the absorption of ginkgolide B from the duodenum to the colon. The results obtained show that passive membrane diffusion predominates in the absorptive transport behavior of ginkgolide B and the pH of the intestine is the critical factor for the absorption of ginkgolide B [86]. Therefore, attempts have been made to use an absorption enhancement strategy and develop a sustained-release preparation of ginkgolide B to enhance the absorption of ginkgolide B by releasing the drug into the upper intestine with a reduction in the ionization of the drug in the lower intestine. Triptolide is one of the most bioactive components of Tripterygium extract, probably followed by tripdiolide. These compounds are responsible for most of the pharmacological effects of the Tripterygium extract. However, other extract components described in a review may, to some degree, augment the pharmacological effects of the extract and modify its pharmacokinetics, bioavailability and toxicological properties [87]. The existence of synergy effects can be detected with a mixture of natural products [88]. Synergistic effects can be produced if the constituents of an extract affect different targets or interact with one another in order to improve the solubility and, thereby, enhance the bioavailability of one or several components of an extract.

Validated methods may be used to assess the bioavailability and pharmacokinetics of a drug [89]. Mammalian P-gp has wide substrate specificity, transporting several drugs with diverse chemical structures, including macrocyclic lactone antiparasitic agents, anticancer agents (vinca alkaloids, doxorubicin) and steroid hormones. Application of a P-gp inhibitor can reduce the efflux and alter the excretion (both urinary and biliary) of some P-gp substrate drugs [90].

5. Conclusion

A survey of the literature related to use of technology for enhancing bioavailability was conducted in order to gain understanding of which methods can be used for this purpose. The focus of the literature reviewed was drug bioavailability, which is a multifactorial process dependent on drug interactions, the gastrointestinal internal environment, physicochemical properties, dosage form, formula and metabolism of the drug molecule. For example, most studies report successful improvement in bioavailability of small molecules extracted from TCMs. Of these studies, instability is often associated with pH and/or enzyme-mediated degradation in the upper gut. These effects can be overcome by formulation approaches such as enteric coating. There is an increasing trend to develop modified-release preparations for some small molecules of TCMs that have low solubility, low permeability, or both. By definition, prodrugs that are devoid of pharmacological activities may be used for increasing drug delivery. Compounds that are too polar are made into inert, lipophilic prodrugs to improve permeability, whereas insoluble compounds are produced as salt prodrugs for added solubility. An increasing body of evidence has shown that certain lipids, and lipid and polymer-based excipients, are capable of inhibiting both presystemic drug metabolism and P-gp-mediated drug efflux by the gut wall. The results suggest a new mechanism that may contribute to the improved bioavailability seen for drugs formulated with lipid-based excipients [91]. With the increased use of herbal remedies, there is the potential for the ingestion of large amounts of constituents that might normally appear in the diet in small amounts, especially the phytoestrogenic isoflavones such as daidzein and genistein. It has long been recognized that the intake of food can alter the rate and extent of drug absorption [92]. More and more new dosage forms are being used to increase the dissolution as well as the bioavailability of natural medical components. For example, the manufacture and formulation of a breviscapine nanosuspension has been discussed to improve the bioavailability for oral administration [93].

In cases where adequate information regarding complicating factors of bioavailability is supplied, however, it is difficult to use a single technique or a single method to enhance bioavailability of small molecules extracted from TCMs. A more comprehensive theoretical analysis of mechanisms of bioavailability enhancement in the drug delivery environment may provide further guidance.

6. Expert opinion

According to the absorption characteristics of natural medical components, this review has discussed the reasons for poor bioavailability and the current technology and delivery systems used to increase bioavailability. It offers a helpful insight into the studies involving the latest research into new herbal drug development. Many new techniques to improve drug bioavailability are being developed rapidly with further research into the mechanisms of action absorption, such as the designing of prodrugs, use of many new drug delivery systems, and application of intestinal metabolic enzymes and efflux pump inhibitors.

6.1 Prodrug modifications

Optimal structural features and physicochemical properties may be associated with bioactivities of the active molecules in the target organ. However, not all molecular forms and properties of drugs are suitable for absorption. To increase all the therapeutic effects of drug molecules, modifications and transformation of the structure of the parent drugs may be needed to improve the absorption properties while retaining the

basic pharmacological effects. A suitable design of prodrugs can protect some drug molecules from enzyme recognition and degradation, increase the liposolubility of highly water-soluble drugs passing through permeable membrane, and enhance the transport function of the lymph circulation for lipophilic drugs. The overwhelming majority of glycosides are believed to be native prodrugs and resist hydrolysis by gastric acid and digestive enzymes. The usual modifiers include polyethylene glycol, dextran and polyamino acids. Current problems affecting modified drugs are their low activity, instability, complex structure and lack of valid synthetic methods. It is proposed that future research in this field will include a search for and the preparation of modifiers and the selection of optimal conditions for naturally occurring drug molecules.

6.2 Application of intestinal metabolic enzymes and efflux pump inhibitors

Many drugs can easily pass through membranes and enter into cells, but they cannot be absorbed completely because of the intestinal mucosal barriers. More and more research and applications are now being focused on the effect of intestinal metabolic enzymes and efflux pumps on drug absorption. Some oral natural medicines are metabolized by enzymes in the intestinal tract, which leads to a first-pass effect and low bioavailability, so intestinal metabolic enzyme inhibitors can be used to promote absorption.

Substrates of P-gp and CYP3A are partly overlapping, and include antineoplastics, hormones, immunosuppressants, protease inhibitors and Digoxin. Among the most commonly used medicines are P-gp inhibitors, such as antiarrhythmic agents, which markedly affect intestinal drug absorption.

After oral administration of Taxol, its bioavailability is low and great differences are seen because of the high affinity for P-gp. Also, the oral bioavailability is significantly increased when Taxol is perfused with a P-gp inhibitor. Among potential P-gp-interfering compounds, the co-administration of the potent CYP3A4 inhibitor, ketoconazole, leads to increased bioavailability of several drugs in a manner consistent with inhibition of intestinal CYP3A4. Flavonoids, a group of polyphenols widely occurring in plants, including flavones such as quercetin, constitute a promising new class of natural modulators of P-gp. Intestinal metabolic enzymes and efflux pump inhibitors offer a high sensitivity and wide range of applications.

6.3 Enhancement of lipophilic properties of drug molecules

Enhancement of lipophilic properties can improve the plasma membrane permeability of highly water-soluble drug molecules and enhance the transport function of lymph circulation for lipophilic drug molecules. Lymph circulation is an important way to increase the intestinal tract transport of fat-soluble vitamins, cholesterin and lipophilic drugs. Some drug molecules are absorbed by the lymph circulation in the intestinal tract, which avoids passing through the portal vein and overcomes the side effects of the gastrointestinal tract and the hepatic first-pass effect. Promoted lymph transport can accelerate the absorption of highly lipophilic, triglyceride-soluble agents and metabolic steady-state of constitutes, so as to improve the bioavailability.

6.4 Applied new drug delivery systems

With the development and fusion of pharmaceutics, materials science and pharmacokinetics over the past few decades, there has been rapid progress in the theory and technological aspects of drug delivery systems. The bioavailability of administered drug molecules has been improved by the design of new delivery systems such as liposomes, microspheres, microcapsules, nanoparticles, cyclodextrin-grafted cellulosic fabric, hydrogels, nanosponges, beads, nanogels/nanoassemblies and cyclodextrin-containing polymers. Some research has also investigated the ability of excipients to enhance drug absorption across biological barriers, the ability to control the rate and time profiles of drug release, drug safety, drug stability, and the ability to deliver drugs to the target site. The pharmaceutical agents, the cyclodextrins, have been found to be very promising for the design of nanoparticles that offer a higher stability and greater surface area because of their small particle size, allowing better contact with the biological membranes, leading to a higher bioavailability. Inclusion with cyclodextrins is a convenient alternative to solve the problems encountered in the administration of hydrophobic drugs; likewise, self-emulsifying drug delivery systems offer a promising approach. This inclusion process leads to changes in the physicochemical properties of natural compounds, such as solubility, dissolution rate and bioavailability.

The difficult problem of herb constituents needs to be solved urgently as far as TCM research is concerned. Recently, the concept of nanoherbs has been put forward and applied, but the physicochemical properties and therapeutic effects of herbs show obvious changes following processes at a nanometer level. Substances in molecularly dispersed form are more efficiently absorbed into the systemic circulation owing to small particles (in the nanometer range) and endocytosis.

Except for the technology mentioned above, drug targeting of intestinal-specific transporters, drug targeting delivery systems and regulatory expressing vectors will improve the absorption and bioavailability of drugs.

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• **The review was useful for interpreting bioavailability and bioefficacy of polyphenols, which are the most common and widely distributed group of TCMs.**

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