Traditional Chinese medicine: saponins, critical micellar concentrations and partition coefficients

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Traditional Chinese medicine: saponins, critical micellar concentrations and partition coefficients

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Abstract

Introduction: Traditional Chinese medicine (TCM) revolves around complex mixtures bound to specific roles within the formulation, among which saponin-containing plants with alleged properties of harmonising or detoxifying other compounds present in the preparations.

Objective: This article deals with the study of these interactions with, as a model, the interaction between saponins and selected active principles.

Methods: The measurement of the partition coefficient between water and octanol (log*P*) was used as an indicator and determined by nuclear magnetic resonance (NMR) for these active principles in the presence of saponins. For each compound, a graph was constructed showing the evolution of log*P* with increasing concentrations of saponins.

Results: Four distinct patterns of interactions were distinguished. Pattern A showed a constant decrease of log*P*, pattern B showed a decrease followed by a plateau, in pattern C the log*P* did not vary until the critical micellar concentration (CMC) and decreased afterwards, and pattern D exhibited an increase of log*P*. These properties were linked to the ability of saponins to form micelles in water once the CMC is reached. The interaction of aconitine and saponins followed pattern D, thus explaining the detoxification of herbal preparations using *Aconitum* with licorice. The licorice facilitated the extraction of the notoriously water-insoluble artemisinin from *Artemisia annua*.

Conclusion: This investigation confirms that the physical properties of micelle forming saponins are intimately linked to a modification of behaviour of the other molecules in solution, as seen with the alteration of log*P* and the four types of interactions presented.

KEYWORDS

aconitine, artemisinin, critical micellar concentration, licorice, partition coefficient, saponins, traditional Chinese medicine

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Dedicated to the memory of Professor Louisette Le Men-Olivier, who initiated work on saponins in Reims

1 | INTRODUCTION

Chinese herbal medicines generally consist of mixtures of a fairly large number of plants, with each of them being assigned a specific role: Sovereign (or Emperor), Minister, Assistant (or Adjuvant) and Courier (or Messenger), also known as the Jun-Chen-Zuo-Shi classification.[1,2] Numerous attempts have been made to extract "heroic principles" from this corpus of plants to include them in the Western pharmacopeia, with little success, a noticeable exception being artemisinin (Qing Hao Su) extracted from *Artemisia annua* L.[3] The main reason for this relative failure lies in a fundamental difference between the two systems of medicine: "one disease-one target-one drug" on the one hand, "target networks-multiple drugs" on the other hand.[4,5] The occidental system revolves around curing a target disease, while traditional Chinese medicine (TCM) aims at restoring balance. Human genome sequencing and a better understanding of genetic interactions have led to a renewal of interest in combination therapy, which will hopefully help to fill the gap between the two systems.[6] Activity against one or several molecular targets might be key to the success of these preparations and the chemical and physical properties of these complex mixtures also contribute to it. The complexity of TCM preparations makes them difficult to study at the molecular level and we simplified the problem by taking as a model, the interactions between saponins and diverse active principles.

The presence of saponin-rich plants in a large variety of preparations is a characteristic of TCM. Table 1 lists some of them (not exhaustively) as well as their role in traditional formulations.[7,8] It should be noticed that, while they can occupy all the four positions of the Jun-Chen-Zuo-Shi classification, saponin-rich plants are most often found in the "Courier" and "Assistant" roles. For instance, the root of *Glycyrrhiza glabra* L., notoriously known to contain saponins, fills the role of Sovereign in the Zhi Gan Cao Tang and Gancao Xiaomai Dazao Tang formulations, while being the Assistant in Xiao Jian Zhong Tang or the Courier in many others (Si Ni Tang, Si Jun Zi Tang, Sang Ju Yin, Xia Qing Long Tang, Shao Yao Gan Cao Tang, Gan Cao Ganjiang Fuling Baizhu Tang, Guizhi Gan Cao Longgu Muli Tang, Zhizi Gan Cao Chi Tang, Houpo Shengjiang Banxia Gan Cao Renshen Tang preparations).

Most authors explain the ubiquitous presence of saponins in TCM by their intrinsic biological properties, but we felt that, in addition to those, the solubilising properties of saponins must also play a key role. The purpose of this work is to investigate the effect of saponins on the bioavailability of drugs and we chose to work on a few saponins representative of plants used in TCM: glycyrrhizin (*Glycyrrhiza glabra*), α-hederin (*Hedera helix* and *Nigella sativa*), β-aescin (*Aesculus hippocastanum*), soyasaponin I (*Glycine max* and *Medicago sativa*), as pure compounds and an extract from *Quillaja saponaria*.

2 | EXPERIMENTAL

2.1 | General experimental procedures

All tested compounds were available from our laboratory or purchased from Sigma-Aldrich or Alfa-Aesar. Millipore water was used and purified 1-octanol was purchased from Prolabo.

2.2 | Sample preparation

Sample preparation required *c.* 2 mg of pure compound which was solubilised in a 5 ml vial with 1.5 ml of a water/deuterated water (H_2O/D_2O) (90:10) saponin solution at different concentrations. Stock solutions of saponins were prepared in H_2O/D_2O (90:10) at 2 g/L for glycyrrhizin, 0.03 g/L for a-hederin, and 0.3 g/L for soyasaponin I, β-aescin, and *Quillaja* saponin. A range of dilutions around the critical micellar concentration (CMC) was prepared from these solutions: 0.02 to 1.28 g/L for glycyrrhizin, 0.002 to 0.03 g/L for α-hederin, and 0.02 to 0.3 g/L for soyasaponin I, β-aescin, and *Quillaja* saponin. Solutions were placed in an ultrasonic bath for 5 to 10 min to optimise solubilisation and filtered on a high-performance liquid chromatography (HPLC) disposable syringe filter from Macherey-Nagel (pore size 0.45 µm). An aliquot (550 µl) of the filtered solution was placed in nuclear magnetic resonance (NMR) tube A for analysis, while 700 µl was placed in an Eppendorf tube for partition against 700 µl of 1-octanol. The Eppendorf tube was inverted at least 40 times, centrifuged at around 2000 rpm for 10 min and left to rest for 24 h to reach equilibrium. A portion (550 µl) from the aqueous phase was then placed into NMR tube B for comparative analysis.

TABLE 1 A list of plant containing saponins used in traditional Chinese medicine (TCM) and their place in the Jun-Chen-Zuo-Shi classification.

Plant species	Role	Plant species	Role
Achyrantes bidentata Blume	Minister	*Dioscorea polystachya* Turcz.	Assistant
Acorus tatarinowii Sol.	Courier	*Foeniculum vulgare* Mill.	Courier
Adenophora tetraphylla A. DC.	Minister	*Forsythia suspensa* Vahl	Courier
Aesculus hippocastanum L.	Sovereign	*Gardenia jasminoides* J. Ellis	Courier
Allium schoenoprasum L.	Sovereign	*Glycyrrhiza glabra* L.	Courier
Amomum villosum Lour.	Assistant	*Indigo tinctoria* L.	Courier
Angelica pubescens Maxim.	Assistant	*Lonicera japonica* Thunb.	Courier
Atractylodes lancea Thunb.	Assistant	*Platycodon grandiflorus* A. DC.	Courier
Cimicifuga heracleifolia Kom.	Courier	*Polygala tenuifolia* Willd.	Assistant
Codonopsis pilosula Franch.	Assistant		

2.3 | NMR procedures

NMR measurements were performed on a Bruker Avance III 600 MHz spectrometer using thin-wall NMR tubes of size 5 mm × 178 mm and equipped with a TCI (triple-resonance inverse with carbon observe) cryoprobe. Peak picking, integration and quantitative NMR were realised on the Topspin software (version 4.0.9) from Bruker. The temperature of the samples was regulated at 298 K. To suppress the solvent, the spectrometer frequency was locked onto D_2O and proton (^1H) spectra were acquired by means of the zgesgp pulse sequence with eight scans per free induction decay (FID) and a 12 s relaxation delay, resulting in a 4 min 55 s recording time. The transmitter frequency offset (O1) was set at water frequency (around 2818 Hz) and gradient ratios (smoothed rectangular shape sequence SMSQ10.100) were fixed to gradients G1 = 31% and G2 = 11%. A 180° shaped pulse (square selective pulse Squa100.1000) was fixed at 180° pulse length p12 = 2 ms and power at 180° shaped pulse SPdB (−dB) = 33 or SPW (W) = 5.01 e^{-4}. The FIDs (64k points, spectral width = 12,000 Hz) were processed with LB = 0.3 Hz. Concentrations in sample NMR tubes A and B were measured with the ERETIC 2 method integrated in the Topspin software from Bruker. For more practical details see Barthel *et al.*[9]

2.4 | Microscopic experiments

Microscopic observations were realised on an inverted Olympus IX70 microscope with a ×100 immersion lens. Aqueous sample solutions were prepared in glass vials at 1.00 g/L (2 mg of sample in 2 ml H_2O) and a drop was deposited on the glass slide. Increasing glycyrrhizin concentrations were added to the sample solutions. Resulting pictures were analysed on the ImageJ software.

2.5 | HPLC analysis

HPLC measurements were performed with an UltiMate 3000 system equipped with Chromeleon software. The column was a C18 250 mm × 4.6 mm with 5 µm particle size from Interchim, and the mobile phase consisted of acetonitrile/H_2O (70:30, *v/v*) with 0.10% formic acid. The flow rate was 1 ml/min, the injection volume was 10 µl, and the column temperature was 30°C; elution duration was 20 min. Detection was made on a ultraviolet (UV) detection diode at a wavelength of 254 nm. For artemisinin, the analysis was made on a lyophilised aqueous extract of *Artemia annua* leaves (courtesy of Pierre Fabre Laboratories) which was prepared from 4 g of dried powdered leaves with a 15 min decoction in 200 ml of boiling pure water. Five similar decoctions were prepared by adding glycyrrhizin (0.04, 0.08, 0.16, 0.32, 0.64 g/L) to the solution. After filtration, the aqueous solutions were lyophilised, and 5 mg of residue were dissolved in 2 ml of HPLC mobile phase. The retention time of artemisinin was detected at 6 min.

3 | RESULTS AND DISCUSSION

3.1 | Measurement of critical micellar concentrations and partition coefficients

Saponins are tensioactive molecules containing a hydrophobic lipidic core (steroid or triterpenoid) coupled with one or several hydrophilic sugar chains. Above a certain concentration, called the CMC, saponins tend to organise themselves into micelles of various sizes and forms.[10] CMCs in water, were measured on our saponin samples, alone and in the presence of a selection of guest molecules featuring the active constituents of drugs (Table 2 and Figure S39). Measurements were carried out with a du Noüy ring tensiometer[11] and the resulting values were in fair agreement with literature values obtained on a plate method tensiometer.[12–15] The presence of guest molecules had little or no effect on the CMC.

According to principles of drug development in the pharmaceutical industry, the bioavailability of drugs is deemed to be linked to partition coefficients between octanol and water (or log*P*).[16] The partition coefficients are usually measured by HPLC. However, for the sake of convenience and due to the very large number of measurements involved, we developed a quicker method based on NMR.[9] This method is sensitive and allowed a large number of analysis since only about 2 mg of compound and a small quantity of D_2O are required (150 µl). To avoid effects due to D_2O as solvent, we chose to use a mixture of H_2O/D_2O (90:10), that allowed valid comparison with reported log*P* measured in H_2O in the literature. The suppression of the residual water peak was performed using water suppression by excitation sculpting (a spin-echo experiment); the dephasing of all coherences set on the water frequency, cleanly and selectively with limiting baseline distortions and phasing issues (about 0.5 ppm around water signal). The ERETIC 2 tool allows a direct quantification of NMR signals with no additional standard. The full list of bioactive molecules representing a selection of drugs from natural or chemical origin is provided in the Supporting Information section (Table S1).

3.2 | Influence of the concentration of glycyrrhizin on partition coefficients

A stock solution of glycyrrhizin (ammonium salt) was made in a mixture of H_2O/D_2O (9:1), dilutions of which were prepared to proceed to measurements below and above its CMC. These dilutions were utilised to prepare sample aqueous solutions and the concentration was determined by ^1H NMR using the ERETIC 2 tool.[9] A part of the solution was partitioned with 1-octanol and the concentration of the aqueous phase was determined in the same manner (Figure 1). The partition coefficient of the sample was calculated from the ratio of these two values with C_w as the concentration in water and C_{wo} that after partition.

$$\log P = \log \frac{C\,(\text{octanol})}{C\,(\text{water})} = \log \frac{Cw - Cwo}{Cwo}$$

TABLE 2 Critical micellar concentration (CMC) of saponin samples with or without guest molecules.

Saponin	Guest molecule	CMC (g/L)	Literature value (g/L)
Glycyrrhizin	-	0.15	0.20
	(+)-Catechin	0.20	
	Caffeine	0.30	
	Acetylsalicylic acid	0.20	
	Ascorbic acid	0.15	
	L-Phenylalanin	0.15	
	L-Tyrosin	0.15	
	Vanillin	0.25	
α-Hederin	-	0.01	0.01
	(+)-Catechin	0.01	
	L-Tyrosin	0.01	
β-Aescin	-	0.10	0.10
	(+)-Catechin	0.06	
Soyasaponin I	-	0.16	0.09
	(+)-Catechin	0.10	
Quillaja saponin	-	0.05	0.14–0.77
	(+)-Catechin	0.06	
	Salicylic acid	0.06	
	Caffeine	0.05	

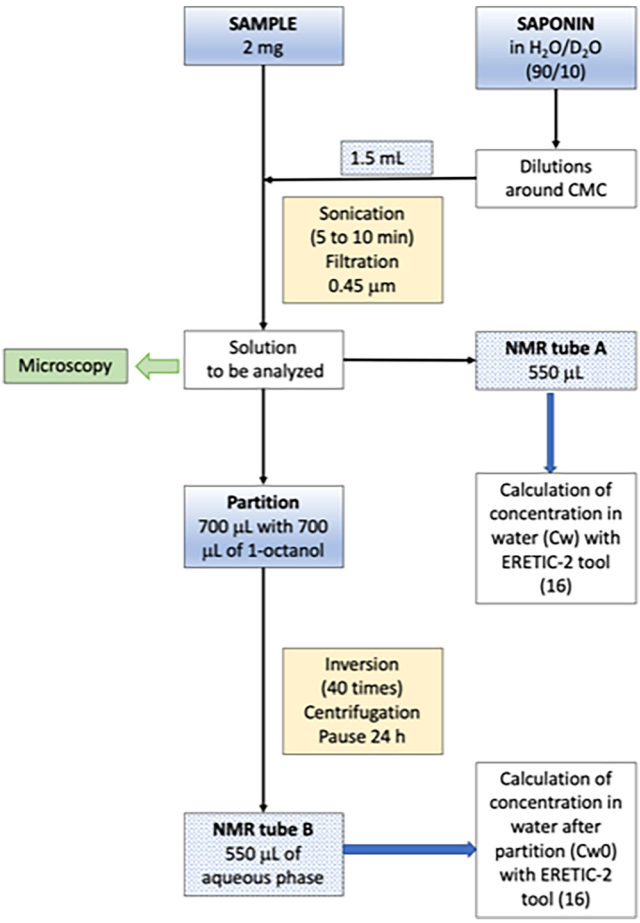

FIGURE 1 Overview of experimental procedure.

Depending on the molecules under study (Table S1), four patterns of behaviour were observed. Pattern A showed a constant decrease of log*P*, therefore a decrease of lipophilicity, as the saponin concentration increased, with no inflexion of the curve at the CMC. Pattern B was characterised by a similar decrease of log*P* until the CMC was reached, followed by a plateau. In pattern C, log*P* did not vary, until an inflexion was observed at the CMC, followed by a continuous decrease. In contrast with the preceding observations, pattern D showed an increase of lipophilicity (a rise in log*P*) until the CMC was reached, followed by a plateau. Examples of representative curves are presented in Figure 2. Although the curves corresponding to patterns A and B bear similarities in their descending parts, they differ in the influence of the micelle formation concentration.

The evolution of log*P* of salicylic acid in the presence of increasing quantities of glycyrrhizin illustrated pattern A (Figure 2a). When the glycyrrhizin concentration was increased from 0 to 3 g/L, the curve showed a decrease of log*P* from 2.5 to 0.5, corresponding to a 100-fold increase in water solubility. This phenomenon may be explained by a decrease of the water superficial tension, which promotes the dispersion of salicylic acid and hence its solubility. Once the CMC was reached, it was observed that the solubility still increased, suggesting a further interaction between the saponin and the molecule, with its incorporation into the micelles. Similar curves were observed for a large variety of compounds: aromatic acids (acetylsalicylic, caffeic, gallic and *p*-coumaric acids), alkaloids (atropine, colchicine and quinine), lawsone, mangiferin, stevioside and rutin (see Supporting Information Figures S1–S11).

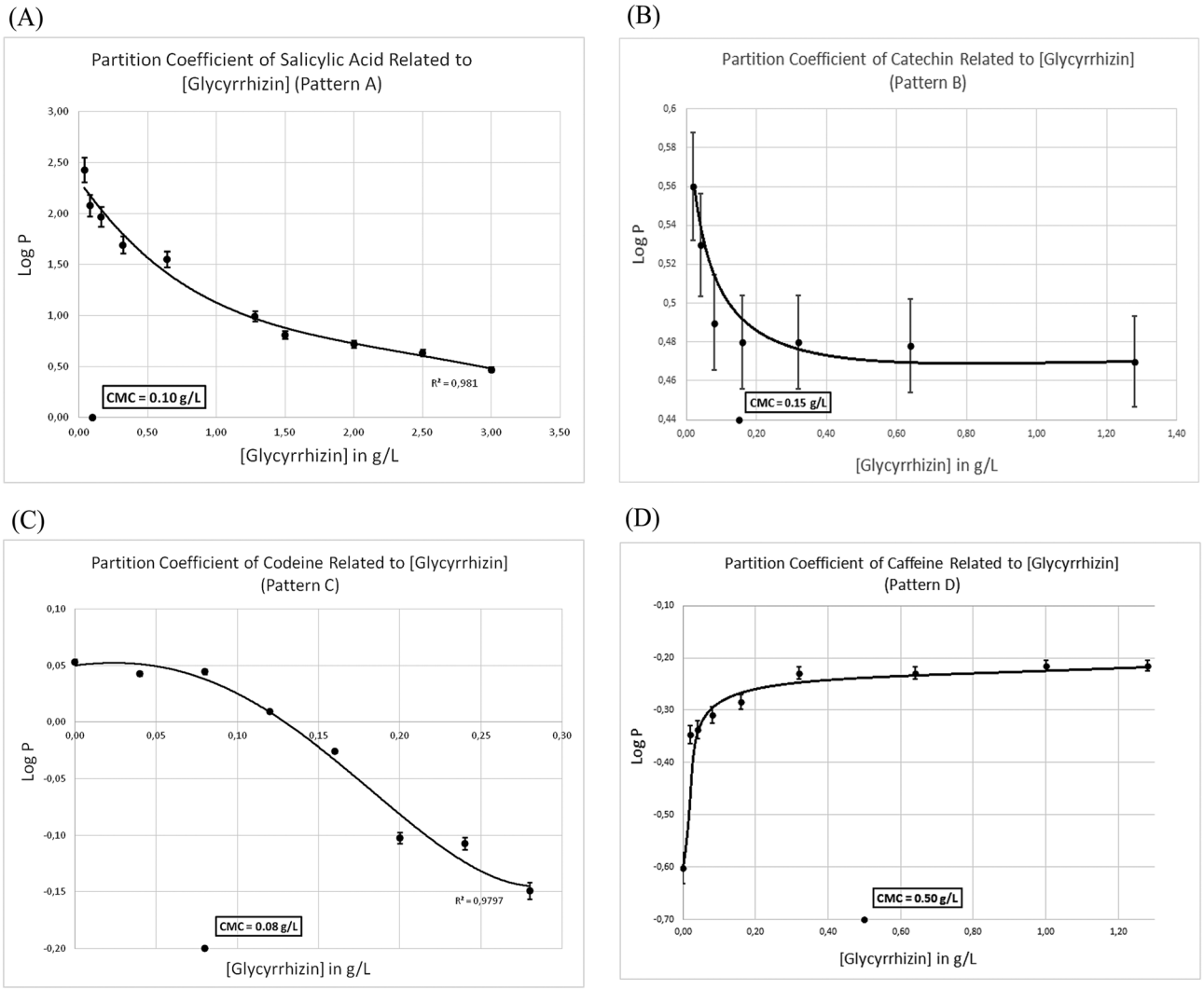

FIGURE 2 Partition coefficient of salicylic acid (a), (+)-catechin (b), codeine (c) and caffeine (d) as a function of glycyrrhizin concentrations.

(+)-Catechin was an example of a curve characterised by a sharp decrease of log*P* until the CMC was reached, followed by a plateau, where no significant evolution of log*P* was observed (Figure 2b). Therefore, it does not seem that micelle formation interferes with the solubilisation process. Once the CMC was reached, superficial tension remained stable and no further solubilisation was observed. Microscopic examination of catechin "solutions" showed the presence of insoluble aggregates, which disappeared upon addition of glycyrrhizin, hence demonstrating its solubilising properties (Figure S30). The same behaviour was observed with the four other saponins. Cinnamaldehyde, cinchonine, cocaine, phenylalanine, tyrosine, theobromine and theophylline gave rise to the same phenomenon (Figures S12–S18).

Molecules with pattern C gave sigmoidal curves with no or little slope until the CMC was reached, followed by a decrease. Thus, log*P* of codeine remained virtually unchanged until the CMC (0.05) and progressively dropped towards −0.25 at three times the CMC (Figure 2c). In this case, the increase in water solubility was directly linked to micelle formation and not to diminished surface tension. Microscopic examination showed that the aggregates corresponding to insoluble material disappeared as soon as micelles were formed (Figure S31). This reaction was observed with morphine, acetaminophen, chlorogenic acid, arbutin, vanillin and zolmitriptan (Figures S19–S25).

A totally opposite behaviour was observed for some molecules, where lipophilicity increased with saponin concentration, because of water dissociation forces becoming weaker than intermolecular forces (Figure 2d). For instance, the couple caffeine/glycyrrhizin, showed an increase in log*P*, from −0.5 to −0.25, reached at the CMC, and with no significant change above it. In this case, the guest molecules become less hydrophilic and more soluble in octanol, as also seen with naringin and capecitabine (Figures S26–S29).

Several compounds such as ascorbic acid did not fit in the picture: its log*P* decreased until the CMC was reached and then increased to a value superior to its initial value (Table S2). This behaviour reflects the ability of ascorbic acid to destabilise micelles and to act as a solvent.[17,18] Molecules of too high or too low lipophilicity did not lend themselves to reliable log*P* measurements with our method and could not be incorporated into this model. They are β-sitosterol, β-carotene,

digitoxin, 18β-glycyrrhetinic acid, docetaxel, myrcene, thymol, amygdalin, curcumin, daidzein, emodin, esculetin, hesperidin, ergotamine and podophyllotoxin.

3.3 | Generalisation with regard to TCM

Salicylic acid was chosen as a type A model compound, due to its presence in several plants from the Chinese pharmacopeia: *Ilicium verum* (star anise), *Peonia lactiflora* (common garden peony), *Isatis tinctoria* (dyer's woad) and *Nelumbo nucifera* (sacred lotus). Its partition coefficient was measured against different concentrations of α-hederin, soyasaponin I, a saponin mixture from *Q. saponaria* and β-aescin (see Figures S32–S35). In the first three cases, the curves showed a profile analogous to the one observed with glycyrrhizin (pattern A), but a pattern B curve was observed with β-aescin, with a plateau after the CMC. Thus, the addition of a saponin containing plant to a plant containing salicylic acid led to a three-fold decrease in lipophilicity of the active principle, therefore to a better aqueous availability. The same four saponins led to similar lipophilicity decreases for (+)-catechin (pattern B) present in common TCM recipes based on *Camellia sinensis* (tea), *Ziziphus jujuba* (Chinese date) and *Cinnamum verum* (cinnamon tree). Chlorogenic acid, one of the active principles of *Andrographis paniculata* (green chiretta), *Salvia miltiorrhiza* (Chinese sage) and *Coptis chinensis* (goldthread) showed drops of log*P* at the CMCs of α-hederin and β-aescin as in pattern C combinations.

The traditional use of saponin-rich plants in TCM formulations fills a specific role in the hierarchy of ingredients. According to the Jun-Chen-Zuo-Shi classification, plants in the Courier role aim to harmonise and detoxify the formulation. Aside from the biological effects of saponins, this investigation confirms that the physical properties of micelle forming saponins are intimately linked to a modification of behaviour of the other molecules in solution, as seen with the alteration of log*P* and the four types of interactions presented earlier. These results agree with previous results on the effects of saponins on water solubility like those reported by Schöpke and coworkers.[19]

3.4 | The aconitine and artemisinin cases

Log*P* of aconitine in the presence of glycyrrhizin showed a sharp decrease until the CMC was reached followed by a less pronounced decrease, typical of pattern B behaviour, meaning that the compound became more water soluble with increasing saponin concentration (log*P* dropped from −0.60 to −1.20, Figure S36). In TCM, plants of the genus *Aconitum* are almost systematically accompanied in the TCM by licorice root as the Courier.[20,21] Since aconitine is a notoriously toxic compound, this suggests that lowering the partition coefficient brings more aconitine into the aqueous phase and thus enhances its urinary excretion, reducing its acute toxicity. This is illustrated by the classical herb-pair Fuzi-Gan Cao (*Aconitum carmichaelii-Radix* and *Rhizoma Glycyrrhizae*) where the cardiotoxicity of the former is attenuated by the later.[22]

Artemisinin, the antimalarial active principle of Qing Hao Su, is so lipophilic that it could only be developed as a single-compound drug as the hemi-succinate (artesunate). It is easily identified by NMR spectroscopy when dissolved in deuterated chloroform ($CDCl_3$) (singlet at 6.00 ppm for the hemiketal proton), whereas it is almost impossible to detect it in an aqueous phase, rendering our method of log*P* measurement ineffective. However, after addition of glycyrrhizin, artemisinin's signal became observable and a log*P* of 1.7 was measured at a 0.28 g/L concentration of the saponin (Figure S37). This last result was also observed in HPLC: the concentration of artemisinin detected in a decoction of 20 g/L of leaves of *Artemisia annua* (retention time 6.1 min) steadily increased after adding glycyrrhizin to the mixture (Figure S38). In other words, saponins had a direct effect on the aqueous extraction of artemisinin by their action on partition coefficients and water solubility. Thus, the relative area percentage of artemisinin in the decoction increased from 3% to 21%, when glycyrrhizin concentration went from 0.08 g/L to 0.32 g/L.

These results explain why the inclusion of licorice roots in traditional formulations has a direct impact on the toxicity and elimination of bioactive molecules such as aconitine, and on the availability of lipophilic molecule such as artemisinin in aqueous formulations.

It remains to understand the nature and the structural aspects of the interactions to predict the behaviour of a given product in the presence of a saponin. Similar interactions prevail in the food domain, which also makes use of complex mixtures of ingredients, as demonstrated by a cryo electron microscopy study of *Quillaja* saponins micelles in the presence of lutein esters.[23] This work is but a small part in the understanding and modernisation of TCM. Recent reviews and reports show major research activity in the promising areas of integrated pharmacology and of multi-component and multi-target mechanisms of actions.[24,25] Efforts are also being made to find a consensus between traditional use and drug-likeness as ruled by Lipinski and coworkers.[26,27] Because of the complexity of the mixtures and the high number of possible interactions from pharmacological and chemical standpoints future investigations will require the use of simplified models like ours.

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DATA AVAILABILITY STATEMENT

Data available upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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