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Review article

Chinese herbs and their molecules: Clinical and pathophysiological implications for the liver

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ABSTRACT

Nature in China is rich in plants that are partially used as medicinal herbs for the treatment of several ailments and facilitated the development of herbal traditional Chinese medicine (TCM) in Chinese communities. Herbal TCM preparations often consist of several different herbs with numerous molecules of organic chemical structure as ingredients. On a molecular basis, some Chinese herbs are known for their hepatotoxic potency with its rare risk of a severe clinical course that requires liver transplantation if acute liver failure develops. The clinical diagnosis of hepatotoxicity by Chinese herbs is challenging due to the lack of diagnostic biomarkers except for the hepatic sinusoidal obstructive syndrome (HSOS), a specific liver disease caused by herbs containing unsaturated pyrrolizidine alkaloids. HSOS is the intrinsic form of liver injury, thereby predictable, reproducible in experimental animals, and dose dependent. Most other cases of liver injury by Chinese herbs are of idiosyncratic nature and experimentally not reproducible, emerge unpredictable, and occur independently of the dose. Injuries seem to be triggered mostly in the smooth endoplasmic reticulum of the liver cell by generation of reactive radicals, which initiate apoptosis and cell destruction. In cases of idiosyncratic liver injury, the individual molecular culprit commonly remains unclear due to herb multiplicity and lacking experimental reproducibility. In addition, the multiplicity of molecules also may cause clinically relevant metabolic interactions at the molecular and hepatocellular level. Thus, although Chinese herbs commonly are well tolerated, consumers should be aware of potential hepatotoxicity and metabolic interactions, preferring herbs with a low risk and an established efficacy.

KEY WORDS: Herbal molecules, traditional Chinese medicine (TCM) – Chinese herbs - intestinal resorption – hepatic metabolism – herb-herb interaction

INTRODUCTION

The use of herbal medicines is based on traditional knowledge and represents a world market for estimated at US$ 60 billion annually [1], according to a UN report dating back to 2000 [2]. Alone in the United States, the total estimated herb retail sales in all channels rose from $ 4.23 billion in 2000 up to $ 6.03 billion in 2013, equaling to 42.6% overall and to 3.3% on an annual basis according to the data of the American Botanical Council [3]. However, actual and robust data are lacking to what extent herbal traditional Chinese medicine (TCM) contributes to these figures worldwide. The United States spent $ 7.6 billion in 2010 on TCM products from China [4], and in Europe exports of TCM products amounted to $ 2 billion [5].

Considering these enormous amounts of herbal TCM preparations that are produced and used worldwide, consumers are flooded by abundant molecules from these Chinese plants that may be differentiated as good ones, bad ones, and ugly ones, in analogy to a classification proposed for herbs in general [6]. The relationship between Chinese herbs with their molecules and Chinese medicine is based on traditional principles, which are highly appreciated in homeland China under strict pharmacovigilance and risk control [7], but there are worldwide discussions around herbal product quality [8,9], efficacy [10-12], and adverse reactions [13,14]. Although questions of efficacy and adverse reactions relate to many diseases, ailments, and organs, the clinical and pharmacological interests of adverse reactions center on the liver as the key metabolic organ [15-18].

In this review article, we focus primarily on the clinical consequences of various Chinese plants with their molecules on the liver, causing potentially hepatotoxic events leading to herb induced liver injury (HILI). Out of the multiple available herbs and their molecules, we chose some few examples to review their particular pathophysiological relevance for these liver injuries.

TCM HERBS AND THEIR MOLECULES

Plants produce active molecules, grow at various extents in most countries of the world, and are the basis of local traditional herbal medicine in their respective cultures. In line with these observations, China is rich in plants [7,8,15,16,19-23], which favored the development of local herbal TCM [7]. About 13000 herbal preparations are used, listed in the Chinese Materia Medica (CMM),and available in China some of them [8,21]; they are officially recognized and described in detail by the Chinese Pharmacopeia and Ministery of Health Standard [8,20], including herbs that are commonly used or represent regional variations and folk medicine variants. The Chinese Materia Medica [20] is a reference book that also describes details of thousands of plant preparations [24], including some nonbotanical

elements such as animal parts and minerals [8,15,24,23], which are incorrectly classified as herbal medicines [8]. Outside of China, only around 500 Chinese herbs are commonly used [8]. The plants of the Chinese Materia Medica contain multiple molecules as hidden champions for the development of potent drugs to be synthetized by the pharmaceutical industry [25].

Whereas modern medicine aims to consider molecular aspects for its diagnostic and therapeutic considerations as far as possible, TCM is based on the ancient TCM philosophy [24,26] and follows a holistic but not a specific molecular approach [7,16]. Therefore, TCM primarily considers plants rather than their individual molecules. TCM philosophy also requires the use of numerous herbal TCM products as mixtures of different herbs, commonly with up to six herbs [17,22] or even more [17]; typically there is a primary herb referred to as the "King" [22] or "Monarch" [8] herb. The other constituents, called also "Minister", "Assistant", or "Envoy" [8], are believed to function as modifiers of toxicity, which is well recognized but not detailed and not described in terms of specific molecular toxins [8,22]; they are also considered to synergistically increase the King herb effects [17], to improve the immune function [22], or strengthen certain aspects of actions [22].

LIVER INJURY FROM CHINESE HERBS, A DIAGNOSTIC AND CLINICAL CHALLENGE

Diagnosis

Cases of herbal TCM hepatotoxicity commonly are published in Chinese, impeding easy and quick access in countries outside of China; for instance, 427 cases have been published from one single Chinese hospital, the Beijing Dital Hospital [16]. Considering reports published mainly in English, a recent study analyzed 77 relevant publications of hepatotoxicity by the use of overall 57 different TCM herbs and herbal mixtures [18]. The further evaluation of the cases of hepatotoxicity by these 57 TCM herbs and herbal mixtures identified 28 herbal products as established culprits of the liver injury cases (Table 1) [18]. Causality was verified by the CIOMS scale (Council for International Organizations of Medical Sciences), positive reexposure test results, or both, and was established for 28/57 different herbs or herbal mixtures. Details of the cases are provided by the original reports as referenced [18] and by other articles [15,17]. For the cases with the remaining 29 TCM herbs and herbal mixtures, information of case data was fragmentary and did not necessarily allow a firm retrospective causal attribution, but the authors of these reports attributed causality for these remaining 29 TCM products according to their personal evaluation [18]. The diagnosis of HILI by the 29 Chinese herbal products requires at least the exclusion of alternative causes, since it is a diagnosis of exclusion [9], but it is often unclear to what extent this was done with the required scrutiny [18].

For suspected HILI by herbal TCM, a valid diagnostic biomarker as test substance in the blood is rarely available [9]. This is because in most cases of TCM hepatotoxicity, liver injury emerges due to an idiosyncratic reaction (Figure 1) and occurs independently of the dose. Idiosyncratic reactions are initiated by only few molecules with free radical characteristics, which remain within the liver cell, do not evade in the circulation, and thereby are not assessable in the blood. Diagnostic conditions are better in cases of hepatotoxicity, which are caused by intrinsic reactions that are dose dependent. Since molecules in large amounts are involved, these or their metabolites are well assessable in the blood and establish the diagnosis. As an example, a sensitive and specific assay exists enabling the detection of a reactive pyrrole-protein adduct in the serum of patients with the hepatic sinusoidal obstructive syndrome (HSOS) due to the use of Chinese herbs that contain unsaturated pyrrolizidine alkaloids (PAs) [27]. The results of this assay show that the patient actually consumed a herb containing unsaturated PAs, which are metabolized in the liver to a reactive PA metabolite, reacting with a protein and forming an adduct [9,27,31]. However, this assay does not prove that PAs have caused the hepatotoxicity in this particular patient, needing supportive evidence in the clinical context [9]. .

Table 1 Selective Chinese herbs or herbal preparations with established causality

Chinese herbs with proven hepatotoxicity
Bai Xian Pi
Bo He
Ci Wu Jia
Chuan Lian Zi
Da Huang
Gan Cao
Ge Gen
Ho Shou Wu
Huang Qin
Hwang Geun Cho
Ji Gu Cao
Ji Xue Cao
Jin Bu Huan,
Jue Ming Zi
Jiguja,
Kudzu
Ling Yang Qing Fei Keli
Lu Cha
Ren Shen
Ma Huang
Shou Wu Pian
Shan Chi
Shen Min,
Syo Saiko To
Xiao Chai Hu Tang
Yin Chen Hao
Zexie
Zhen Chu Cao

Adapted data from a previous report [18]

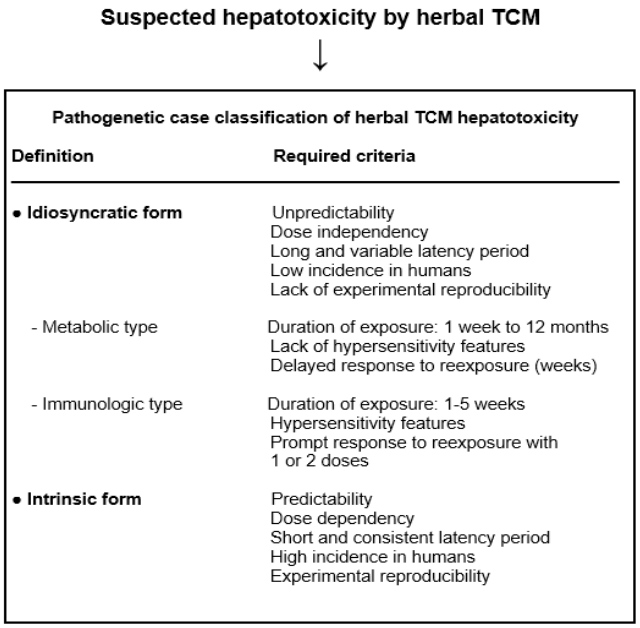

Figure 1. Pathogenetic classification of herbal TCM hepatotoxicity

To clarify a causal relationship between an acute liver disease of a patient and the previous use of an herbal TCM may be cumbersome and is a particular clinical challenge, since a temporal association alone is not sufficient to construct a valid causal association. Patients with hepatotoxicity by drugs or herbs present typical characteristics that can be captured and scored, and the sum of the individual scores clarifies whether a causal association is highly probable, probable, possible , unlikely, or excluded [9]. For this approach, the hepatotoxicity specific CIOMS scale is recommended, either as its original [28,29] or better its update [30].

Clinical course

The clinical course of idiosyncratic HILI by herbal TCM is variable [9,16] and may be severe with acute liver failure in 19.4% of the cases [16]; in most cases, liver injury develops slowly with clinical symptoms such fatigue, jaundice, anorexia, nausea and fever [16] that are similar to cases of HILI by modern herbal medicine and of DILI by synthetic drugs [9].

Of note, the clinical features are different in patients with HSOS caused by Chinese herbs containing unsaturated PAs such as Tu San Qi, also complicated by a high lethality [31]. Prevailing symptoms of HSOS are malaise, abdominal distension and pain, hepatomegaly, jaundice, and ascites [31], while ascites is uncommon in the other cases of hepatotoxicity by TCM herbs not containing unsaturated PAs [16]. Actually, the reported HSOS cases were attributed to the Tu San Qi preparation made erroneously with Gynura sedum containing unsaturated PAs instead with Segetum aizoon lacking PAs [27].

For cases of hepatotoxicity by herbal TCM, some details of treatment modalities are provided, with focus on daily and cumulative dose, treatment duration, latency period, and reexposure duration; details are reported for aloe [32], two not further described Chinese herbal mixtures [33,34], Chinese Jin Bu Huan [35], Chinese Syo Saiko To [36], green tea (GT), syn. Lu Cha and Camellia sinensis [37,38], and Polygonum multiflorum [39], as summarized in Table 2 [40].

Cessation of herbal use is the only therapeutic approach for patients with HILI by TCM, since other options including evidence based therapies are lacking [9]. With cessation of herbal use, clinical signs usually vanish along with improvements or normalization of initially increased liver values [15]. A well described dechallenge of liver values in suspected HILI is one of the key items to suspect causality for a particular herb. Patients with HILI caused by herbal TCM commonly experience an acute type of liver injury, which is self-limited upon withdrawal of the offending herb with an overall good prognosis [15]. In few instances, patient with the acute type of HILI may progress to acute liver failure. This is a serious condition that commonly requires a liver transplant and eventually leads to death [41-44]. Between 1992 and 2008 and alone in Seoul (Korea), 24 patients underwent liver transplantation due to toxic herbal hepatitis mostly related to TCM products [44], causing concern in view of poorly documented efficacy of herbal TCM products [12,45].

HAZARDOUS HEPATOTOXIC MOLECULES DERIVED FROM CHINESE HERBS

General aspects

TCM herbs are classified as having various degrees of toxicity, but these are not specified regarding organ or molecular culprit [16]. In the Chinese Medical Pharmacopeia [20], herbs are described as mildly toxic to highly toxic, with 83 items of CMM in the latter category [8,20]. Since robust experimental data are lacking, the herbal TCM philosophy related to toxic elements is elusive; although known for a long time [16], it appears that the question of herbal toxicity has not yet been fully appraised. Also, the use of nonherbal items (animal parts or heavy metals) as elements of the ancient herbal TCM philosophy is difficult to assess regarding their specific toxicity [8,15-17,24].

On a molecular basis, various hepatotoxins of TCM herbs are described in the literature [6,8,15,16,22,31], but systematic toxicology studies on all herbal TCM are still lacking that could provide information of toxic doses and limiting doses [16]. With the exception of some few well documented dose related liver injuries [15,27,31,47-52], no differentiation is commonly made in most reports whether liver injury was based on a dose unrelated idiosyncratic reaction or a dose dependent intrinsic reaction (Figure 1); occasionally, both reaction types were mixed up [6,8,15,16]. These shortcomings also apply to some herbs with their chemical compounds of the actual listing (Table 4), as compiled mainly from data

of a previous study [16]. At present, two different potential hepatotoxic compounds merit further consideration, namely epigallocatechin-3-gallate (EGCG) contained in green tea extracts (GTE) [47-50] and unsaturated PAs as ingredients of various Chinese herbs [27,31,51,52]. Both chemicals share the dose dependency of their hepatotoxic potency and will be discussed in detail since they are of clinical interest. The clinical features caused by these two compounds are different, as are the pathophysiological events leading to their liver injury.

Catechins of green tea extracts

Prepared from the leaves of the plant Camellia sinensis, which has been cultivated in China and other Southeast Asian countries, GT is a popular beverage since thousands of years [53] and well tolerated [48-50]. However, molecules of catechins derived from GT leaves may be hepatotoxic in humans when used as overdosed GTE [48-50]; this dose dependent liver injury was confirmed for EGCG as the major constituent of GT leaves in experimental animals [47].

Table 2. Some characteristics of daily and cumulative doses, treatment duration, latency period, and reexposure period of cases with hepatotoxicity by TCM herbs

Case	Sex Age	Herb Herbal mixture	Daily dose	Cumulative dose	Treatment duration	Latency period	Reexposure duration	References
1.	F/62y	Aloe	420 mg	37800 mg	3.0 mo	2.75 mo	1.0 mo	Yang et al., 2010 [32]
2.	F/39y	Chinese herbal mixture	n.a.	n.a.	2.0 mo	2.0 mo	0.1 mo	Kane et al., 1995 [33]
3.	F/9y	Chinese herbal mixture	n.a.	n.a.	6.0 mo	5.25 mo	1.0 mo	Davies et al., 1990 [34]
4.	F/66y	Chinese Jin Bu Huan	0-2 tablets	60 tablets	3.0 mo	2.75 mo	0.5 mo	Woolf et al., 1994 [35]
5.	M/46y	Chinese Jin Bu Huan	0-3 tablets	216 tablets	6.0 mo	6.0 mo	1.0 mo	Woolf et al., 1994 [35]
6.	F/52y	Chinese Syo Saiko To	7.5 g	338 g	1.5 mo	1.5 mo	1.0 mo	Itoh et al., 1995 [36]
7.	F/58y	Chinese Syo Saiko To	7.5 g	675 g	3.0 mo	3.0 mo	0.25 mo	Itoh et al., 1995 [36]
8.	F/42y	Chinese Syo Saiko To	7.5 g	158 g	0.75 mo	0.75 mo	0.07 mo	Itoh et al., 1995 [36]
9.	F/56y	Green tea	14 ml	210 ml	4.0 mo	3.3 mo	1.0 mo	Jimenez-Saenz and Martinez-Sanchez, 2006 [37]
10.	F/37y	Green tea	n.a.	n.a.	4.0 mo	4.0 mo	1.0 mo	Bonkovsky, 2006 [38]
11.	M/61y	*Polygonum multiflorum*	n.a.	n.a.	0.033 mo	0.033 mo	0.033 mo	Jung et al., 2011 [39]

In all 11 hepatotoxicity cases, causality for the respective herbs or herbal mixture was ascertained by positive reexposure test results based on established criteria. Abbreviations: mo, months; n.a., not available. Adapted data from a previous report [40],

Table 3. Selective compilation of hepatotoxic substances of herbal TCM

Chinese name	Scientific name	Proposed hepatotoxic components
Ai Ye	*Artemisia argyi*	Volatile oil
Bi Ma Zi	Rhicinus communis	Ricin, toxic proteins
Cang Er Zi	*Xanthium*	Glycosides (kaurene), diterpenoids
Chang Shan	*Dichor febrifuga Lour*	Alkaloids (dichroine)
He Huan Pi	*Albizia julibrissin*	Glycosides (saponine)
He Shou Wu	*Polygonum multiflorum*	Anthraquinones
Huang Yao Zi	*Discorea bulbifera L.*	Glycosides (steroids, diosgenin), Diterpenoids-lactones
Ku Lian Zi	Melia azedarach	Glycosides (tetranortriterpenoids)
Lei Gong Teng	*Tripterygium wilfordii hook*	*F* Glycosides (tripterygium), Diterpenoid-lactones
Lu Cha	*Camellia sinensis*	(-)-epigallocatechin-3-gallate
Qian Li Guang	*Senecio scandens*	Pyrrolizidine alkaloids
Shang Lu	*Phytolacca acinosa Roxb.*	Alkaloids (phytolaccine)
Xiang Si Zi	*Abrus Precatorius*	Abrin

Data of the Chinese herbs were compiled from the report of Ma et al., 2014 [16], except those of Lu Cha (Camellia sinensis, green tea), which were based on the reports of Lammert et al. [47], of Navarro et al. [48], and the NIH [49], as summarized recently [50]

Table 4. Modification of human cytochrome P450 isoforms by GT, GTE, and their individual catechin constituents

Green tea/ Green tea extracts/ catechins	Clinical/ experimental conditions	Parameter
Green tea (GT)	NR	NR
Decaffeinated Green tea (dGT)	Clinical study: oral use of capsules for 4 weeks	Human CYP activity CYP1A2 → [54] CYP2C9 → [54] CYP2D6 → [54] CYP3A4 (↓) [54]
	Clinical study: oral use of capsules for 2 weeks	Human CYP activity CYP2D6 → [55] CYP3A4 → [55]
Green tea extracts (GTE)	In vitro study: human hepatic microsomes	Human CYP activity CYP2C8 ↓ [56] CYP2B6 ↓ [56] CYP2C9 ↓ [57] CYP2C19 ↓ [56] CYP2D6 ↓ [56,57] CYP3A ↓ [56] CYP3A4 ↓ [57]
	In vitro study: human intestinal microsomes	Human CYP activity CYP3A4 ↓ [56]
Epigallocatechin-3-gallate (EGCG)	In vitro study human hepatic microsomes	Human CYP activity CYP2B6 ↓ [56] CYP2C8 ↓ [56] CYP2C19 (↓) [56] CYP2D6 (↓) [56] CYP3A ↓ [56]
	In vitro study: human intestinal microsomes	Human CYP activity CYP3A4 ↓ [56]
	In vitro study: membrane fraction of genetically engineered Salmonella typhimurium TA 1538 cells harboring human liver CYP	Human CYP activity CYP1A1 ↓ [58] CYP1A2 ↓ [58] CYP3A4 ↓ [58] CYP2A6 ↓ [58] CYP2C19↓ [58] CYP2E1↓ [58]
Epicatechin (EC)	In vitro study: membrane fraction of genetically engineered Salmonella typhimurium TA 1538 cells harboring human liver CYP	Human CYP activity CYP1A1 ↓ [58] CYP1A2 ↓ [58] CYP3A4 ↓ [658
Epicatechin-3 gallate (ECG)	In vitro study: membrane fraction of genetically engineered Salmonella typhimurium TA 1538 cells harboring human liver CYP	Human CYP activity CYP1A1 ↓ [58] CYP1A2 ↓ [58] CYP3A4 ↓ [58]
Epigallocatechin (EGC)	In vitro study: membrane fraction of genetically engineered Salmonella typhimurium TA 1538 cells harboring human liver CYP	Human CYP activity CYP1A1 ↓ [58] CYP1A2 ↓ [58] CYP3A4 ↓ [58

Abbreviation: CYP, cytochrome P450; GT, green tea; GTE, green tea extract; NR, not reported. Modification from a previous report [50], based on various publications [54-58].

Therefore, human hepatotoxicity by GTE is classified as an intrinsic type of injury according to required criteria (Figure 1) [9]. Consensus exists that GT use is not associated with hepatotoxic risks when consumed as usual beverage in normal doses [48-50], confirmed by a search in the regulatory database of the China Food and Drug Administration revealing no hepatic safety data regarding GT under these conditions of use [50].

Experimental studies showed that overdosed GTE and its catechins cause increased lipid peroxidation and oxidative stress in the liver [47], suggesting that the liver injury may result from the generation of injurious free radicals [48]. Major scientific interest in GT, GTE, and their catechins led to numerous studies on cytochrome P450 (CYP) (Table 4) [50,54-58], hepatic and intestinal drug metabolism, microbial metabolism, excretion, absorption, distribution, bioavailability, and pharmacokinetics [50]. Currently, there is no evidence that CYP is involved in catechin metabolism via a phase I reaction [59], but catechins may modulate their own phase II degradation and possibly influence bioavailability and metabolism of other drugs but not their

potential hepatotoxicity [50].

Camellia sinensis leaves have been used as herbal TCM to treat various ailments, since multiple positive features of GT have been postulated concerning antiarthritic, antibacterial, antiviral, antiinflammatory, antiangiogenic, neuroprotective, and cholesterol-lowering effects, including prevention of cancer and cardiovascular diseases [50,60]. However, the clinical efficacy of prophylactic and therapeutic measures largely remains unproven due to the lack of appropriate evidence-based clinical trials [50].

Unsaturated pyrrolizidine alkaloid containing Chinese herbs

Chinese herbs containing unsaturated PAs [61] exert a major clinical and hepatotoxicity problem [9,27,31,51,52]. The molecular basis of hepatotoxicity by unsaturated PAs is complex and has been elucidated in experimental studies, which showed the involvement of phase I and II metabolizing enzymes; for phase I, the hepatic microsomal CYP 3A and 2B isoforms are required in both C-oxidation and N-oxidation of the necine base to form the reactive pyrrolic ester metabolites and pyrrolizidine alkaloid N-oxides, respectively. The dehydropyrrolizidine alkaloids (pyrrolic ester) metabolites are chemically and biologically reactive and tend to undergo further biotransformations; once formed, the pyrrolic ester metabolites can rapidly bind with DNA, leading to DNA cross-linking, DNA-protein cross-linking, and DNA adduct formation [52]. These adducts can then be quantified in the serum of patients who took herbal unsaturated PAs [27,31]. So far, little attention has been paid that hepatotoxicity occurs only by the use of unsaturated but not the unsarurated PAs [61]. The difference between the two types is a single double bond, missing in the saturated form and present in the unsaturated form. Many more plants have unsaturated PAs and only few saturated PAs [61].

On a molecular level, unsaturated PAs are good examples for the intrinsic form of liver injury, which is clearly dose dependent, thereby predictable, and hence preventable (Figure 1). HSOS is the typical disease type of liver injury caused by usaturated PAs since their metabolites obstruct the hepatic sinusoids by damaging their endothelial cells [9,27,31], representing a particular risk for all individuals who consume herbs containing unsaturated PAs [9], including herbs of TCM with unsaturated PAs [51]. Unsaturated PA containing plants are probably the most common poisonous plants affecting not only humans but also livestock and wildlife, with more than 6.000 plants containing PAs and about 3% of the world's flowering plants containing PAs [52]. Some of these plants have caused toxic liver disease, recognized as epidemics and sometimes primarily assigned to viral hepatitis and not necessarily to toxic plants [9]. Human embryotoxicity with HSOS caused by unsaturated PAs has been described in a newborn whose mother drank one cup of a tea containing PAs per day throughout pregnancy [9,52]. On a worldwide basis, some PA containing plants may be listed as examples such as Crotalaria species (Bush tea, Rattlebox), Ilex paraguarensis (Mate tea), Symphytum species (Comfrey), Senecio species (Groundsel), Heliotropium species, and Compositae species (Indian herbs) [9]; for each individual species, proof is needed whether the plant contains unsaturated PAs, since species differences exists [61]. A total of 49 species of Chinese plants containing PAs have been identified [51] but the respective PA form [61] was not specified [[51]; all these plants are listed in the Traditional Chinese Dictionary and are used as folk remedy or medicinal TCM herbs in China for various purposes [51]. These include cerebral stroke, malaria, tuberculosis, measles, common cold, gastroenteritis, diarrhea, dysentery, dysmenorhoe, pains, fever, rheumatism, skin diseases with ulcer, wounds and inflammation, ascariasis, oxyuriasis, and even infantile malnutrition and hepatitis; they are also used for their presumed antipyretic, antiphlogistic, and hemostatic effects [51].

Metabolic interactions at the molecular and hepatic level

Drug-herb and herb-herb interactions are major scientific issues and of potential clinical relevance, considering both herbs of TCM and non-TCM herbs [6,62,63], or specifically TCM herbs [64-66] such as the TCM Lu Cha (Camellia sinensis) and its catechins [50,54,55]. Metabolic interactions in patients consuming herbal TCM are inevitable for several reasons. First, any TCM herb has numerous individual chemicals as constituents, and these molecules may easily interact with each other, when they reach the liver or even before in the intestinal mucosa at the time of their uptake, as shown for instance for catechins [50,54,55] with involvement of hepatic and intestinal CYP (Table 4). Second, individuals using a TCM herb often take other TCM herbs or herbal mixtures [15,50], and are thereby flooded by numerous molecles, which may cause metabolic interactions due to multimedication. Whereas other herbs are often administered in combination with synthetic drugs [66], users of TCM herbs rarely take synthetic drugs [15,60]. Although many metabolic interactions have been reported with clinical relevance, most of them are from case reports and limited clinical observations [66]. Further studies on pharmacokinetics and pharmacodynamics will improve our understanding of these complex adverse reactions and contribute to risk minimizing. Presently, risks of metabolic interactions are best reduced by avoiding concomitant use of multiple TCM herbs.

Future developments

Molecular aspects of TCM herbs are to be discussed in relation to the rare liver injury associated with their use, but TCM herbs are much more fascinating in the context of future drug research and development based on plants as natural producers of chemical substances [9]. There are

great expectations that in the future more synthetic drugs are developed, based on herbal ingredients being effective in human diseases [25]. In fact, for most of history, herbal medicine was the only available medicine. It has also been estimated that one third to one half of currently used drugs were originally derived from plants [68]. Encouraging developments are underway [69], with focus on herbal TCM and its improved disease management [67, 70-74]. There is no question that among the multiple medicinal herbs and their molecules, many hidden champions will emerge in the near future as active chemicals for human use and disease treatment.

Concluding remarks

Molecules are basic chemicals essential for herbal TCM at various levels. First, they can assist in elucidating mechanisms of rare intrinsic liver injuries by Chinese herbs in some cases, providing thereby basic tools of diagnosing these specific diseases. Although the present impact of molecules is yet limited, perspectives are encouraging when more herbal molecules are identified as active compounds to be used for specific diseases, considering their molecular basis and receptor characteristcs. Second, a good understanding of molecular principles of herbal product actions and disease targets with specific receptors will allow further research on new molecule based drugs and facilitate the development of molecule based modalities of disease treatment, undergoing clinical trials to proof efficacy and evaluate the benefit/risk profile. Therefore, molecular considerations will improve TCM conditions and facilitate TCM globalization. Some time is needed for the transition from ancient herbal TCM to modern TCM meeting the requirements of modern medicine regarding therapy efficacy and safety. Progress of TCM modernization has already been made and led to promising perspectives.

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