

## Traditional Chinese Medicine and herbal hepatotoxicity: a tabular compilation of reported cases

Rolf Teschke,<sup>\*</sup> Li Zhang,<sup>†</sup> Hongzhu Long,<sup>‡</sup> Alexander Schwarzenboeck,<sup>\*</sup> Wolfgang Schmidt-Taenzer,<sup>\*</sup> Alexander Gentner,<sup>\*</sup> Albrecht Wolff,<sup>§</sup> Christian Frenzel,<sup>||</sup> Johannes Schulze,<sup>¶</sup> Axel Eickhoff<sup>\*</sup>

<sup>\*</sup>Department of Internal Medicine II, Division of Gastroenterology and Hepatology, Klinikum Hanau, Teaching Hospital of the Medical Faculty of the Goethe University Frankfurt/ Main, Germany.

<sup>†</sup>Center for Drug Reevaluation, China Food and Drug Administration, Beijing, China.

<sup>‡</sup>Department of Internal Medicine, Dongfang Hospital, Beijing University of Chinese Medicine, Beijing, China.

<sup>§</sup>Department of Internal Medicine II, Division of Gastroenterology, Hepatology and Infectious Diseases, Friedrich Schiller University Jena, Germany.

<sup>||</sup>Department of Medicine I, University Medical Center Hamburg Eppendorf, Germany.

<sup>¶</sup>Institute of Industrial, Environmental and Social Medicine, Medical Faculty of the Goethe University Frankfurt/Main, Germany.

### ABSTRACT

Traditional Chinese Medicine (TCM) with its focus on herbal use became popular worldwide. Treatment was perceived as safe, with neglect of rare adverse reactions including liver injury. To compile worldwide cases of liver injury by herbal TCM, we undertook a selective literature search in the PubMed database and searched for the items Traditional Chinese Medicine, TCM, Traditional Asian Medicine, and Traditional Oriental Medicine, also combined with the terms herbal hepatotoxicity or herb induced liver injury. The search focused primarily on English-language case reports, case series, and clinical reviews. We identified reported hepatotoxicity cases in 77 relevant publications with 57 different herbs and herbal mixtures of TCM, which were further analyzed for causality by the Council for International Organizations of Medical Sciences (CIOMS) scale, positive reexposure test results, or both. Causality was established for 28/57 different herbs or herbal mixtures, 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, Rhen Shen, Ma Huang, Shou Wu Pian, Shan Chi, Shen Min, Syo Saiko To, Xiao Chai Hu Tang, Yin Chen Hao, Zexie, and Zhen Chu Cao. In conclusion, this compilation of liver injury cases establishes causality for 28/57 different TCM herbs and herbal mixtures, aiding diagnosis for physicians who care for patients with liver disease possibly related to herbal TCM.

**Key words.** Herb induced liver injury. Council for International Organizations of Medical Sciences. Herbs. Causality assessment. Re-exposure.

### INTRODUCTION

Traditional Chinese Medicine (TCM) and in particular its herbal sector is popular in China<sup>1</sup> and many countries worldwide.<sup>2-4</sup> For most traditional herbal treatments, there is insufficient rigorous scientific evidence about the efficiency of herbal TCM

for their claimed indications,<sup>3</sup> usually due to lack of research publications in English. Consequently, additional controlled clinical trials are needed to evaluate their efficacy and risk profile including scientific publications, preferentially in English.<sup>5</sup> In Western countries, herbal TCM is considered as natural and erroneously thereby assumed to be safe, delaying recognition of possible side effects and timely treatment discontinuation. Although side effects by herbal TCM in general are rare and mostly transient upon treatment cessation, hepatic adverse reactions may be life threatening, requiring a liver transplant, or both.<sup>6-8</sup>

This concise article presents for the first time a comprehensive tabular compilation of all potentially hepatotoxic herbal TCMs. These are individually identified by respective references published since

Correspondence and reprint request: Rolf Teschke, M.D.  
Professor of Medicine. Department of Internal Medicine II.  
Klinikum Hanau, Academic Teaching Hospital of the Goethe University of  
Frankfurt/Main  
Leimenstrasse 20, D-63450 Hanau, Germany  
Tel.: +49-6181/21859  
E-mail: rolf.teschke@gmx.de

*Manuscript received: July 17, 2014.*

*Manuscript accepted: August 25, 2014.*

1986. Additional information is provided for the names of the authors, the year of publication, and the overall number of reported cases. Other tabular compilations present results of individual causality assessments by liver specific algorithms and positive reexposure test results.

## LITERATURE SEARCH

To collect all cases of liver injury by herbal TCM, a selective literature search in the PubMed database was performed. We used the search items Traditional Chinese Medicine, TCM, Traditional Asian Medicine, and Traditional Oriental Medicine alone and combined with the terms herbal hepatotoxicity, or herb induced liver injury.

The search was primarily focused on English-language case reports, case series, and clinical reviews, published from 1984 to 15 March, 2014. From each search, the first 25 publications being the most relevant publications were analyzed for subject matter, data quality, and overall suitability. All citations in these publications were searched for other yet unidentified case reports.

## TRADITIONAL CHINESE MEDICINE

TCM is no single entity but encompasses different practices including acupuncture, moxibustion, massage, dietary therapy, and physical exercise such as shadow boxing, with herbal medicines as the most important section.<sup>1-3</sup> In Western countries, the use of the name TCM remained unchanged, in recognition of the tradition originating from ancient China. Therefore, we used the term Traditional Chinese Medicine (TCM) pragmatically as a general term since a regional differentiation would introduce unwanted selection bias effects unrelated to the herbal ingredients. TCM in this review therefore combines Traditional Asian Medicine (TAM), Traditional Oriental Medicine (TOM), Traditional Korean Medicine (TKM), and Traditional Kampo Medicine (TKM) since the principles are identical or vary little between countries. Using TCM as the generic term facilitates and focuses discussions of TCM related issues.

## COMPILATION OF RELEVANT CASES

We identified 57 different herbs and herbal mixtures of TCM with potential liver injury in 77 case reports and case series (Table 1); their clinical case details were presented earlier.<sup>9-87</sup> Such a detailed compilation of cases has not been published before

and it may assist clinicians and practitioners evaluating patients with suspected hepatotoxicity by the use of herbal TCM. Three additional reports of hepatotoxicity cases following herbal TCM use were excluded from table 1 because details of the applied herbs were missing.<sup>88-90</sup> The figure of 57 different herbs and herbal mixtures compares with 582 medicinal herbs of the Chinese Materia Medica (CMM), which are available in China and are officially recognized and described in detail by the Chinese Pharmacopeia.<sup>91,92</sup> If all herbs of widespread use, regional variations, and folk medicine are included, then the total increases to around 13,000 CMM preparations currently in use in China.<sup>91,93</sup> Since our review is based on English language case reports, many more than the presently 57 different herbs and herbal mixtures of TCM with potential hepatotoxicity likely exist. This implies that reports in Chinese or other languages are not included, as they are difficult to locate, difficult to evaluate due to language barriers, and difficult to reassess. Nevertheless, a few abstracts have been included in our analysis, if provided in English and considered essential. Consequently, our analysis facilitates wide accessibility and promotes reevaluation but likely covers only a minority of the truly existing cases.

Botanical names of herbs are provided, which were used individually or as combination partners of herbal mixtures (Table 1). These names were retrieved from the published reports and verified through an internet search. The herbs were not always further specified, because relevant data often were contradictory and insufficiently described in the publications. One TCM name may be used for various preparations in China, but not necessarily in other countries. Among these are prepared decoction pieces (known as Yin Pian), extracts or granules of the decoction pieces (known as Keli), as well as unprepared and crude material.<sup>1</sup> Of particular importance are Proprietary Chinese Medicines (PCM) products known as Zhong Cheng Yao, which must be approved by the China FDA before marketing.<sup>1</sup> Unapproved PCM products are regarded illegal medicines and are commonly of poor quality, shortcomings likely applying to other countries as well.

The reference list for the reports mentioned in table 1 allows information for number and period of publication. In the years 1984 to 1993, 1994 to 2003, and 2004 to 2013, there were 2, 20, and 55 publications for the respective periods. With 28 and 27 publications for 2004 to 2008 and for 2009 to 2013, the publication frequency was stable within the last decade. Hepato-

Table 1. Compilation of reported cases with suspected hepatotoxicity by herbal Traditional Chinese Medicine.

Name with ingredients	Cases (n)	References
An Shu Ling <i>Lycopodium serratum</i> or, rarely, <i>Corydalis species</i> , <i>Panax ginseng</i> , <i>Pseudo ginseng</i> , or two species of <i>Stephania</i>	1	Haller, <i>et al.</i> , 2002 <sup>9</sup>
Bai Fang <i>Angelica sinensis</i> , <i>Cyperus rotundus</i> , <i>Ginseng</i> , <i>Ligusticum wallichii</i> , <i>Paeonia alba</i> , <i>Rehmannia glutinosa</i>	1	Estes, <i>et al.</i> , 2003 <sup>10</sup>
Bai Shi Wan <i>Atractylis</i> , <i>Carthamus tinctorius</i> , <i>Dalbergia odorifera</i> , <i>Dioscorea bulbifera</i> , <i>Glycyrrhiza</i> , <i>Lithospermum erythrorhizon</i> , <i>Paeonia suffruticosa</i> , <i>Polygonum multiflorum</i> , <i>Psoralea corylifolia</i> , <i>Salvia miltiorrhiza</i> ; <i>Endoconcha sepiae</i> , <i>Ganoderma lucidum</i> (mushroom)	1	Talari, <i>et al.</i> , 2010 <sup>11</sup>
Bai Xian Pi <i>Dictamnus dasycarpus</i>	1	Perharic-Walton/Murray, 1992 <sup>12</sup>
	1	Kane, <i>et al.</i> , 1995 <sup>13</sup>
	1	Vautier/Spiller, 1995 <sup>14</sup>
	2	Yuen, <i>et al.</i> , 2006 <sup>15</sup>
	4	Jang, <i>et al.</i> , 2008 <sup>16</sup>
	14	Kang, <i>et al.</i> , 2008 <sup>17</sup>
	2	Sohn, <i>et al.</i> , 2008 <sup>18</sup>
Ban Tu Wan <i>Angelica sinensis</i> , <i>Chaenomeles</i> , <i>Codonopsis pilosula</i> , <i>Notopterygium</i> , <i>Polygonum multiflorum</i> , <i>Rehmannia</i> , <i>Schisandra</i>	1	Cortez, <i>et al.</i> , 2012 <sup>19</sup>
Bo He <i>Mentha haplocalyx</i>		
Bo Ye Qing Niu Dan <i>Tinospora crispa</i>	2	Sangsuwan, <i>et al.</i> , 2004 <sup>20</sup>
Bofu Tsu Sho San <i>Angelica</i> , <i>Atractylis</i> , <i>Cnidium</i> , <i>Gardenia</i> , <i>Ephedra</i> , <i>Forsythia</i> , <i>Glycyrrhiza</i> , <i>Gypsum fibrosum</i> , <i>Lebedouriella</i> , <i>Mentha</i> , <i>Paeonia</i> , <i>Platycodon</i> , <i>Rheum</i> , <i>Schizonepeta</i> , <i>Scutellaria</i> , <i>Zingiber</i> ; <i>Kadinum</i> (talcum powder), sodium sulfuricum	1	Motoyama, <i>et al.</i> , 2008 <sup>21</sup>
Boh Gol Zhee <i>Psoralea corylifolia</i>	1	Hwang, <i>et al.</i> , 2001 <sup>22</sup>
	1	Nam, <i>et al.</i> , 2005 <sup>23</sup>
	3	Cheung, <i>et al.</i> , 2009 <sup>24</sup>
Cang Er Zi <i>Xanthium sibiricum</i>	na	Chau, 2008 <sup>25</sup>
Chai Hu <i>Bupleurum falcatum</i>	28	Lee, <i>et al.</i> , 2011 <sup>26</sup>
Chaso <i>Camellia sinensis</i> , <i>Cassia tora</i> (syn. <i>Senna</i> ), <i>Crataegus</i> , <i>Chrysanthemum morifolium</i> Ramat., <i>Lotus</i> , <i>Lycium barbarum</i> ; N-nitroso-fenfluramine	27	Adachi, <i>et al.</i> , 2003 <sup>27</sup>
Chi R Yun <i>Breynia officinalis</i>	2	Lin, <i>et al.</i> , 2002 <sup>28</sup>
	19	Lin, <i>et al.</i> , 2003 <sup>29</sup>
Chinese herbal mixtures (various) <i>Dictamnus dasycarpus</i> , <i>Gentiana scabra</i> , <i>Hedysarum diffusa</i> , <i>Paeonia suffruticosa</i> , <i>Paris polyphylla</i> , <i>Rehmannia glutinosa</i> , <i>Smilax glabra</i> , <i>Sophora subprostrata</i> ; <i>Angelica sinensis</i> , <i>Bupleurum chinense</i> , <i>Dictamnus dasycarpus</i> , <i>Paeonia suffruticosa</i> , <i>Philodendron chinense</i> , <i>Saposhnikovia divaricata</i> , <i>Shisandra chinensis</i> , <i>Shizonepeta tenuifolia</i> , <i>Tribulus terrestris</i> ; <i>Coccus trilobus</i> , <i>Dictamnus dasycarpus</i> , <i>Eurysolem gracilis</i> , <i>Glycyrrhiza</i> , <i>Lophatherum</i> , <i>Paeonia</i> , <i>Potentilla</i> , <i>Rehmannia glutinosa</i> ; <i>Alisma plantago aquatica</i> , <i>Artemisia capillaris</i> , <i>Bupleurum</i> , <i>Chrysanthemum morifolium</i> , <i>Circuma</i> , <i>Gardenia jasminoides</i> , <i>Gentiana scabra</i> , <i>Glycyrrhiza</i> , <i>Magnolia</i> , <i>Paeonia</i> , <i>Plantago asiatica</i> , <i>Saussurea lappa</i>	1	Perharic-Walton/Murray, 1992 <sup>12</sup>
Chuan Lian Zi <i>Melia toosendan</i>	2	Kane, <i>et al.</i> , 1995 <sup>13</sup>
Ci Wu Jia <i>Acanthopanax senticosus</i>	1	Vautier/Spiller, 1995 <sup>14</sup>
Da Chai Hu Tang <i>Bupleurum falcatum</i> , <i>Ginseng</i> , <i>Glycyrrhiza glabra</i> , <i>Pinellia</i> , <i>Scutellaria</i> , <i>Zingiber officinale</i> , <i>Ziziphus jujuba</i>	1	Yoshida, <i>et al.</i> , 1996 <sup>30</sup>
Da Huang <i>Rheum palmatum</i>	1	Yuen, <i>et al.</i> , 2006 <sup>15</sup>
Du Huo <i>Angelica archangelica</i>	1	Björnsson, <i>et al.</i> , 2013 <sup>32</sup>
Fu Fang Qing Dai Wan <i>Angelica dahurica</i> , <i>Isatis indigotica</i> ( <i>Indigo naturalis</i> ),	1	Verucci, <i>et al.</i> , 2002 <sup>33</sup>

<i>Massa medicata fermentata (yeast), Salvia miltiorrhiza, Smilax glabra</i>			
<b>Gan Cao</b> <i>Glycyrrhiza uralensis</i> , syn. Liquorice	1	Yuen, et al., 2006 <sup>15</sup>	
<b>Ge Gen</b> <i>Pueraria lobata</i> , syn. Arrowroot	2	Kim, et al., 2009 <sup>34</sup>	
<b>Ho Shou Wu</b> <i>Polygonum multiflorum</i> , syn. He Shou Wu	1	Yuen, et al., 2006 <sup>15</sup>	
	1	Bae, et al., 2010 <sup>35</sup>	
<b>Hu Bohe You</b> <i>Mentha pulegium</i> , syn. Pennyroyal oil	na	Chau, 2008 <sup>25</sup>	
<b>Hu Zhang</b> <i>Polygonum cuspidatum</i>	na	Chau, 2008 <sup>25</sup>	
<b>Huang Qin</b> <i>Scutellaria baicalensis</i>	19	Gono, et al., 2010 <sup>36</sup>	
	2	Linnebur, et al., 2010 <sup>37</sup>	
	1	Yang, et al., 2012 <sup>38</sup>	
	1	Dhanasekaran, et al., 2013 <sup>39</sup>	
<b>Huang Yao Zi</b> <i>Dioscorea bulbifera</i>	na	Chau, 2008 <sup>25</sup>	
<b>Hwang Geun Cho</b> <i>Corydalis speciosa</i>	1	Kang, et al., 2009 <sup>40</sup>	
<b>15Ji Gu Cao</b> <i>Abrus cantoniensis</i>	1	Yuen, et al., 2006 <sup>15</sup>	
<b>Ji Ji</b> <i>Chloranthus serratus</i>	na	Chau, 2008 <sup>25</sup>	
<b>Ji Xue Cao</b> <i>Centella asiatica</i> , syn. Gotu Kola	3	Jorge/Jorge, 2005 <sup>41</sup>	
<b>Jiguja</b> <i>Hovenia dulcis</i>	1	Sohn, et al., 2008 <sup>18</sup>	
	1	Kang, et al., 2008 <sup>17</sup>	
	1	Kim, et al., 2012 <sup>42</sup>	
<b>Jin Bu Huan</b> <i>Lycopodium serratum</i> or, rarely, <i>Corydalis</i> species, <i>Panax ginseng</i> , Pseudo ginseng, or two species of <i>Stephania</i>	7	Woolf, et al., 1994 <sup>43</sup>	
	3	Horowitz, et al., 1996 <sup>44</sup>	
	1	Picciotti, et al., 1998 <sup>45</sup>	
	1	Divinsky, 2002 <sup>46</sup>	
	1	Haller, et al., 2002 <sup>9</sup>	
	1	Yuen, et al., 2006 <sup>15</sup>	
<b>Jue Ming Zi</b> <i>Cassia obtusifolia</i> , syn. <i>Senna obtusifolia</i>	1	Inoe, et al., 2011 <sup>47</sup>	
<b>Kamishoyosan</b> <i>Angelica sinensis</i> , <i>Atractylodes lancea</i> , <i>Bupleurum falcatum</i> , <i>Gardenia</i> , <i>Glycyrrhiza glabra</i> , <i>Mentha haplocalyx</i> , <i>Moutan</i> , <i>Paeonia alba</i> , <i>Sclerotium Poriae Cocos</i> , <i>Zingiber officinale</i>	17	Lee, et al., 2011 <sup>26</sup>	
<b>Kudzu</b> <i>Pueraria thunbergiana</i>	6	Kang, et al., 2008 <sup>17</sup>	
<b>Lei Gong Teng</b> <i>Tripterygium wilfordii</i> Hook	na	Chau, 2008 <sup>25</sup>	
<b>Long Dan Xie Gan Tang</b> <i>Acebia</i> , <i>Alisma</i> , <i>Angelica sinensis</i> , <i>Bupleurum</i> , <i>Gardenia</i> , <i>Gentiana</i> , <i>Glycyrrhiza</i> , <i>Plantago</i> , <i>Rehmannia</i> , <i>Scutellaria</i>	17		
<b>Lu Cha</b> <i>Camellia sinensis</i> , syn. Chinese green tea	1	Garcia-Moran, et al., 2004 <sup>48</sup>	
	1	Peyrin-Biroulet, et al., 2004 <sup>49</sup>	
	1	Gloro, et al., 2005 <sup>50</sup>	
	1	Javaid/Bonkovsky, 2006 <sup>51</sup>	
	1	Jimenez-Saenz, et al., 2006 <sup>52</sup>	
	1	Bonkovsky, 2006 <sup>53</sup>	
	1	Molinari, et al., 2006 <sup>54</sup>	
	5	Björnsson/Olsson, 2007 <sup>55</sup>	
	3	García-Cortés, et al., 2008 <sup>56</sup>	
	34	Sarma, et al., 2008 <sup>57</sup>	
	36	Mazzanti, et al., 2009 <sup>58</sup>	
	1	Rohde, et al., 2011 <sup>59</sup>	
	47	Navarro, et al., 2013 <sup>60</sup>	
<b>Ma Huang</b> <i>Ephedra sinica</i>	1	Nadir, et al., 1996 <sup>61</sup>	
	1	Borum, 2001 <sup>62</sup>	
	3	Estes, et al., 2003 <sup>10</sup>	
	1	Skoulidis, et al., 2005 <sup>63</sup>	
	1	Reuben, et al., 2010 <sup>64</sup>	
<b>Mao Guo Tian Jie Cai</b> <i>Heliotropium lasiocarpum</i>	4	Culvenor, et al., 1986 <sup>65</sup>	
<b>Onshido</b> <i>Aloe</i> , <i>Camellia sinensis</i> , <i>Crataegus</i> ,	141	Adachi, et al., 2003 <sup>27</sup>	

<i>Gynostemma pentaphyllum makino, Raphanus; N-nitroso-fenfluramine</i>			
<i>Qian Li Guang Senecio scandens</i>	na	Chau, 2008 <sup>25</sup>	
<i>Ren Shen Panax ginseng</i>	6	Kang, <i>et al.</i> , 2008 <sup>17</sup>	
<i>Sairei To Alisma, Atractylis, Bupleurum, Cinnamomum, Ginseng, Glycyrrhiza, Pinellia, Polyporus, Poria, Scutellaria, Zingiber, Zizyphus</i>	1	Aiba, <i>et al.</i> , 2007 <sup>66</sup>	
	1	Tsuda, <i>et al.</i> , 2010 <sup>67</sup>	
<i>Shan Chi Gynura segetum</i>	2	Dai, <i>et al.</i> , 2006 <sup>68</sup>	
	1	Chen, <i>et al.</i> , 2007 <sup>69</sup>	
	1	Li, <i>et al.</i> , 2010 <sup>70</sup>	
	52	Lin, <i>et al.</i> , 2011 <sup>71</sup>	
	116	Gao, <i>et al.</i> , 2012 <sup>72</sup>	
<i>Shen Min</i> Black cohosh, Burdock, Cayenne pepper, <i>Ginkgo biloba</i> , Horse chestnut, <i>Piper nigrum</i> , <i>Polygonum multiflorum</i> , <i>uva ursi</i> ; biotin, collagen (hydrolyzed), niacin, pantothenic acid, silica (from plant sources), soy isoflavones, vitamin A, vitamin B <sub>6</sub>	1	Cárdenas, <i>et al.</i> , 2006 <sup>73</sup>	
<i>Shi Can Teucrium chamaedrys</i> , syn. Germander	na	Chau, 2008 <sup>25</sup>	
<i>Shi Liu Pi Pericarpium granati</i>	na	Chau, 2008 <sup>25</sup>	
<i>Shou Wu Pian Achyranthes bidentata, Cuscuta chinensis, Eclipta prostrata, Ligustrum lucidum, Lonicera japonica, Morus alba, Polygonum multiflorum, Psoralea corylifolia, Rehmannia glutinosa, Rosa laevigata, Sesemum indicum, Siegesbeckia orientalis</i>	1	But, <i>et al.</i> , 1996 <sup>74</sup>	
	1	Park, <i>et al.</i> , 2001 <sup>75</sup>	
	1	Battinelli, <i>et al.</i> , 2004 <sup>76</sup>	
	1	Panis, <i>et al.</i> , 2005 <sup>77</sup>	
	3	Sohn, <i>et al.</i> , 2008 <sup>18</sup>	
	1	Laird, <i>et al.</i> , 2008 <sup>78</sup>	
	1	Furukawa, <i>et al.</i> , 2010 <sup>79</sup>	
	1	Valente, <i>et al.</i> , 2010 <sup>80</sup>	
	25	Jung, <i>et al.</i> , 2011 <sup>81</sup>	
	1	Banarova, <i>et al.</i> , 2012 <sup>82</sup>	
<i>Tian Hua Fen Trichosanthes kirilowii</i>	na	Chau, 2008 <sup>25</sup>	
<i>White flood</i> Qian Ceng Ta ( <i>Huperzia serrata</i> ), Wu Zhu Yu ( <i>Evodia rutaecarpa</i> ); beet root, caffeine, cocoa bean, vinpocetine (from Vinca plant); acesulfame potassium, calcium silicate, carnitine tartrate, Carno-Syn® beta-alanine, citrulline, cryptoxanthin, folic acid, gamma-aminobutyric acid (GABA), glucuronolactone, selenium, L-norvaline, L-tyrosine, lutein, malic acid, ornithine, potassium gluconate, sucralose, sugar cane, watermelon flavor, zeaxanthin	1	Cohen, <i>et al.</i> , 2012 <sup>83</sup>	
<i>Wu Bei Zi Galla chinensis</i>	na	Chau, 2008 <sup>25</sup>	
<i>Xi Shu Camptotheca acuminata</i>	na	Chau, 2008 <sup>25</sup>	
<i>Xiao Chai Hu Tang Bupleurum falcatum, Ginseng, Glycyrrhiza glabra, Pinellia tuber, Scutellaria baicalensis, Zingiber officinale, Zizyphus jujuba</i>	4	Itoh, <i>et al.</i> , 1995 <sup>84</sup>	
	19	Lee, <i>et al.</i> , 2011 <sup>26</sup>	
	1	Hsu, <i>et al.</i> , 2006 <sup>85</sup>	
<i>Yin Chen Hao Artemisia capillaris</i>	7	Kang, <i>et al.</i> , 2008 <sup>17</sup>	
	1	Sohn, <i>et al.</i> , 2008 <sup>18</sup>	
<i>Zexie Alisma orientalis</i>	1	Yuen, <i>et al.</i> , 2006 <sup>15</sup>	
<i>Zhen Chu Cao Phyllanthus urinaria</i>	1	Yuen, <i>et al.</i> , 2006 <sup>15</sup>	

Data are retrieved from a selective literature search for published cases of herbal TCM associated with suspected hepatotoxicity. In some cases, causality for individual herbs and herbal mixtures was established using the Council for International Organizations of Medical Sciences (CIOMS) scale or its modifications, and by positive reexposure test results. For other cases, information was fragmentary and did not necessarily allow a firm causal attribution. Details are provided by the original reports referenced above and by other articles.<sup>86,87</sup>

toxicity by herbal TCM is reported from many countries around the world with various publications<sup>9-90</sup> from China, 4; Hong Kong, 5; Taiwan, 4; Japan, 9; Korea, 10; Thailand, 1; Australia, 2; Slovakia, 1; Italy, 5; Spain, 3; France, 2; the Netherlands, 1; the

United Kingdom, 4; Denmark, 1; Iceland, 2; Canada, 2; the United States, 20; and Argentina, 1.

Herbal hepatotoxicity is not limited to herbal TCM but also occurs worldwide with numerous other herbs.<sup>7,8</sup> Among sixty different herbs or herbal

mixtures with hepatotoxic potential identified in a recent study, which analyzed 185 published reports, only few were TCM herbs.<sup>7</sup> Overt differences of hepatotoxicity between TCM herbs and non TCM herbs are lacking in clinical presentation, types of liver injury, latency period, dechallenge characteristics, and reexposure characteristics, when comparing the original publications for the present analysis (9-85) with those of the previous publications.<sup>7,8</sup> Both groups have a similar incidence of severity, liver transplantation, and lethal outcome.

## CAUSALITY ASSESSMENT

In patients with suspected herbal liver injury by TCM, the key question is the diagnostic validity. Hepatotoxicity requires strict criteria, best defined by alanine aminotransferase (ALT) and/or alkaline phosphatase (ALP) values.<sup>94,95</sup> Its increase is converted into multiples of the upper limit of their normal range, given as N. For ALT, hepatotoxicity has been defined as increases of  $> 2N$ ,  $> 3N$  or  $> 5N$ , while ALP values of  $> 2N$  are commonly considered diagnostic.<sup>96,97</sup> Restricting only ALT increases of  $> 5N$  as diagnostic eliminates false positive cases and substantiates causality at a higher level of probability. Considering ALT  $> 2N$  as hepatotoxic will include numerous patients with nonspecific increases, with higher requirements for thorough assessment and more stringent exclusion of causes unrelated to the herb(s) under discussion. Also for low threshold N values, more diagnostic alternatives must be ruled out; missing an exclusion of a hepatotoxicity case results in overdiagnosing and over-reporting with false high case numbers.<sup>96</sup> Commonly an ALT cutoff point of 5N is used, or an ALT cutoff of 3N if the total bilirubin exceeds 2N; for ALP, 2N is considered an appropriate definition criterion.<sup>96,97</sup> These criteria are likely fulfilled by most reports included in this review, even considering that N values are rarely mentioned, and some publications do not mention any liver values at all.<sup>9-85</sup> Applying these criteria, the herbal TCM Ba Jiao Lian (*Dysosma pleianthum*) was not proven hepatotoxic, although this was initially assumed.<sup>86,98</sup> Therefore, Ba Jiao Lian is not included as a hepatotoxin in this review of TCM. Valid diagnostic biomarkers in patients with suspected herbal hepatotoxicity currently are lacking,<sup>8</sup> except for pyrrolizidine alkaloids (PAs) where quantification of protein adducts and GSH conjugates in the blood allows intake quantification.<sup>72,86</sup> Considering these limitations and the need of early evaluation of suspicious cases, the best

approach for quick assessment is the combination of clinical judgement and a liver specific causality assessment algorithm like the scale of CIOMS (Council for International Organizations of Medical Sciences), also called RUCAM (Roussel Uclaf Causality Assessment Method).<sup>94,95</sup> This CIOMS scale has been used in cases of herbal TCM hepatotoxicity and commonly provides high quality classifications of highly probable and probable cases initially (Table 2) or after reassessment.<sup>99</sup> In some cases, a previous CIOMS version<sup>100</sup> or a modified CIOMS version<sup>101</sup> was used for assessment (Table 2). Although commonly recommended,<sup>102</sup> overall CIOMS based evaluations were done in only 18 reports (Table 2), not in the remaining 59 publications analyzed in the present review (Table 1). In the future, therefore, all suspected cases should undergo CIOMS assessment to improve case data evaluation.

## REEXPOSURE

A positive reexposure test result commonly is considered as the gold standard to verify the diagnosis of herb induced liver injury.<sup>86,99,103</sup> Since reexposure tests are unintentional and therefore not planned in advance, these cases also have to be analyzed in retrospect. Consequently, under these circumstances case data often are of poor quality, lacking basic criteria for a positive test result. In 25 cases of suspected herbal TCM hepatotoxicity, the authors claimed a positive reexposure test (Table 3); however, in only 14 cases this result was confirmed upon reassessment, when specific and accepted criteria were applied (Table 3).<sup>86,99</sup> In the remaining nine patients, the evaluation was either negative or uninterpretable. Intentional reexposure tests are unethical and obsolete due to high risks.

## CAUSALITY VERIFICATION

Among the reported cases of herbal hepatotoxicity (Table 1), causality was verified by CIOMS scale grades, positive reexposure tests, or both for 27 different herbs and herbal mixtures (Tables 2 and 3), out of a total of 57 (Table 1). These included 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, Juguja, Kudzu, Ling Yang Qing Fei Keli, Lu Cha, Rhen Shen, Ma Huang, Shou Wu Pian, Shan Chi, Shen Min, Syo Saiko To, Xiao Chai Hu Tang, Yin Chen Hao, Zexie, and Zhen Chu Cao. Causality was also established in two un-

**Table 2.** Reported causality assessment by the CIOMS (Council for International Organizations of Medical Sciences) scale in cases of assumed herbal hepatotoxicity by Traditional Chinese Medicine.

Product name	CIOMS causality gradings	CIOMS scores	Cases (n)
Bai Xian Pi	Probable	6-8	2 <sup>18</sup>
	na	na	14 <sup>17</sup>
Bo He	Probable	6-8	1 <sup>15</sup>
Chinese herbal mixtures	Probable	8	1 <sup>88,99</sup>
	Possible	5	1 <sup>12,99</sup>
	Excluded	-1	1 <sup>16,99</sup>
Ci Wu Jia	Probable	6-8	1 <sup>18</sup>
	Possible	3-5	1 <sup>18</sup>
Chuan Lian Zi	Highly probable	> 8	1 <sup>15</sup>
Da Huang	Highly probable	> 8	1 <sup>15</sup>
Gan Cao	Probable	6-8	1 <sup>15</sup>
Ge Gen	Highly probable	10	2 <sup>34</sup>
Ho Shou Wu	Highly probable	> 8	1 <sup>15</sup>
	Highly probable	10	1 <sup>35</sup>
Huang Qin	Possible	5	1 <sup>38,99</sup>
Ji Gu Cao	Possible	3-5	1 <sup>15</sup>
Ji Xue Cao	na	na	3 <sup>41</sup>
Jin Bu Huan	Probable	8	2 <sup>43,99</sup>
	Probable	6	1 <sup>44,99</sup>
	Possible	4	1 <sup>44,99</sup>
Jue Ming Zi	Highly probable	> 8	1 <sup>15</sup>
Juguja	Probable	6	1 <sup>42</sup>
	Possible	3-5	1 <sup>18</sup>
Kudzu	na	na	6 <sup>17</sup>
Ling Yang	Probable	6-8	1 <sup>15</sup>
Qing Fei Keli			
Lu Cha	Highly probable	9	1 <sup>49,99</sup>
	Highly probable	9	2 <sup>55</sup>
	Highly probable	> 8	2 <sup>56</sup>
	Probable	8	1 <sup>52,99</sup>
	Probable	8	2 <sup>55</sup>
	Probable	7	1 <sup>53,99</sup>
	Probable	6-8	1 <sup>56</sup>
	Probable	6	1 <sup>55</sup>
	Possible	3-5	1 <sup>50</sup>
	na	na	6 <sup>17</sup>
Ma Huang	Possible	4	1 <sup>61,99</sup>
Shou Wu Pian	Highly probable	> 8	10 <sup>81</sup>
	Highly probable	> 8	1 <sup>79</sup>
	Probable	6-8	15 <sup>81</sup>
	Probable	6-8	2 <sup>18</sup>
	Possible	3-5	1 <sup>18</sup>
Shan Chi	Highly probable	9	1 <sup>71</sup>
	Probable	7	2 <sup>72</sup>
	Probable	6	1 <sup>72</sup>
	Possible	5	2 <sup>72</sup>
Shen Min	Probable	6-8	1 <sup>73</sup>
Syo Saiko To	Highly probable	9	1 <sup>84,99</sup>
	Probable	8	1 <sup>84,99</sup>
	Probable	6	2 <sup>84,99</sup>
Yin Chen Hao	Probable	6-8	1 <sup>18</sup>
	na	na	7 <sup>17</sup>
Zexie	Highly probable	> 8	1 <sup>15</sup>
Zhen Chu Cao	Possible	3-5	1 <sup>15</sup>

For the listed numbers of cases, the respective publication is provided as superscript. Most listed cases were assessed by the Council for International Organizations of Medical Sciences (CIOMS) scale,<sup>94,96</sup> single cases by an earlier CIOMS version<sup>100</sup> or by a modified CIOMS version.<sup>101</sup> In some original reports, CIOMS causality grading was presented without any individual CIOMS score, so the range of the scores was provided in this table rather than an accurate score number. In one publication of a case series, data of the scores were presented only as means<sup>17</sup> and therefore classified in the table as not available, since individual scores were not provided. Abbreviation: na, not available.

**Table 3.** Causality reassessment of positive reexposure test results initially reported in original publications for cases of herbal hepatotoxicity by Traditional Chinese Medicine.

Product name	Reexposure test conditions (reassessed)	Test results (reassessed)	Cases (n)
Chinese herbal mixtures	ALTb < 5N, ALTr ≥ 2 ALTb ALTb and ALTr not available	Positive Uninterpretable	2 <sup>13,88</sup> 1 <sup>12</sup>
Ho Shou Wu	Not assessable	Uninterpretable	1 <sup>35</sup>
Hwang Geun Cho	ALTb < 5N, ALTr ≥ 2ALTb	Positive	1 <sup>17</sup>
Ji Xue Cao	ALTb < 5N, ALTr ≥ 2ALTb ALTb not available	Positive Uninterpretable	1 <sup>41</sup> 1 <sup>41</sup>
Jin Bu Huan	ALTb < 5N, ALTr ≥ 2 ALTb ALTb ≥ 5N, ALTr < 2 ALTb ALTb < 5N but ALTr < 2 ALTb	Positive Negative Negative	2 <sup>43</sup> 1 <sup>44</sup> 1 <sup>44</sup>
Lu Cha	ALTb < 5N, ALTr ≥ 2ALTb ALTb < 5N but ALTr not available ALTb and ALTr not available	Positive Uninterpretable Uninterpretable	3 <sup>49,52,53</sup> 1 <sup>56</sup> 2 <sup>56,57</sup>
Ma Huang	ALTb and ALTr not available	Uninterpretable	1 <sup>61</sup>
Shou Wu Pian	ALTb < 5N, ALTr ≥ 2ALTb	Positive	2 <sup>77,81</sup>
Xiao Chai Hu Tang	ALTb < 5N, ALTr ≥ 2 ALTb ALTb < 5N but ALTr < 2 ALTb	Positive Negative	3 <sup>84</sup> 1 <sup>84</sup>

For the listed numbers of cases, the respective publications are provided as superscripts. Clinical details and laboratory values were obtained from the original reports, which all described a positive reexposure test result without providing specific criteria. For all 25 cases, reassessment of the reexposure test data was done applying established and strict criteria,<sup>86,99</sup> and the reassessed test results are presented in the table. These results showed a positive causality only in 14 cases, without firm causality in nine cases as claimed in the original reports. Criteria for the hepatocellular type of liver injury<sup>99,103</sup> are the ALT levels at baseline before reexposure (ALTb), and the ALT levels during reexposure (ALTr). Response to reexposure is considered positive if ALTr ≥ 2ALTb and ALTb < 5N, with N as the upper limit of the normal value. Other combinations result in negative causality or uninterpretable results. ALT: alanine aminotransferase. n: upper limit of normal.

classified Chinese herbal mixtures (Table 2), from five mixtures initially included (Table 1).

### HERBAL MISIDENTIFICATION, CONTAMINATION, AND ADULTERATION

It is well recognized that herbal products conform only to fewer quality standards than chemical drugs.<sup>7,8,104,105</sup> This also applies to most herbal TCM products used worldwide.<sup>94,91,106-108</sup> In China, strict regulations exist for China FDA approved herbal TCM products, ameliorating this problem.<sup>1</sup>

In the presently analyzed reports, botanical authenticity of individual herbal ingredients mostly was not published, with exceptions related to An Shu Ling,<sup>9,86</sup> Chi R Yun (*Breynia officinalis*) and Yi Yi Qiu (*Securinega suffruticosa*),<sup>28,29,68-72,86,109,110</sup> Jin Bu Huan and Hua Nan Yuan Zhi (*Polygala chinensis*),<sup>43,44</sup> Shan Qi (*Gynura segetum*) and Jing Tian San Qi (*Sedum aizoon*),<sup>68-72,86,109,110</sup> Shan Qi (*Gynura segetum*) and Mao Guo Tian Jie Cai (*Heliotropium lasiocarpum*),<sup>65,111,112</sup> as well as Shou Wu Pian.<sup>74</sup> For some herbal TCM products, problems have been identified in misidentification on package insert<sup>43,44,60,106</sup> including mistaken herb identity,<sup>28,29,44,65,68-72,86,108-113</sup> and insufficient sample amounts.<sup>113</sup>

Another concern for human use is the possible contamination with dust, pollens, insects, rodents, parasites, microbes, fungi, moulds, toxins, and pesticides.<sup>107,113</sup> Also reported was contamination with hepatotoxic seeds<sup>20</sup> as well as heavy metals such as arsenic, mercury, and lead.<sup>86,107,113</sup> These shortcomings are well recognized<sup>1-4</sup> and require stringent controls by producers and regulatory agencies.<sup>1</sup> Analyses for contamination were rarely done, except for the

herbal mixtures Chaso and Onshido, where contamination with heavy metals like copper, lead, bismuth, cadmium, antimony, tin, mercury, and chromium was not found.<sup>27</sup> Contaminants also were lacking in Jin Bu Huan.<sup>43,44</sup> In other Chinese herbal mixtures, aflatoxins,<sup>12</sup> fungi,<sup>12</sup> heavy metals,<sup>12</sup> and PAs were excluded,<sup>16</sup> but insect fragments (*Cryptotympane pustulata*) were present in the preparations.<sup>12</sup> The TCM Hai Piao Xiao (*Endoconcha sepiiæ*) and Ling Zhi (*Ganoderma lucidum*, mushroom) are listed as ingredients of Bai Shi Wan (Table 1).<sup>11</sup>

Even (criminal) adulterations of herbal TCM products with synthetic drugs not declared as such have been published.<sup>1,25,91,106,107</sup> Analysis for possible adulterants were rarely done and usually negative.<sup>43,44</sup> Adulteration of the herbal TCM products Chaso and Onshido<sup>27</sup> and other TCM products<sup>14</sup> by the synthetic N-nitroso-fenfluramine was found,<sup>15,27</sup> but its hepatotoxic property has not been established.<sup>27,86</sup> N-nitroso-fenfluramine therefore is merely an adulterant that is not related to liver injury<sup>86</sup> observed in the reported cases.<sup>15,27</sup> Neither Chaso nor Onshido are registered by the China FDA; but were produced by Chinese manufacturers and exported to Japan until retracted from the market.<sup>27</sup> Actually, China FDA has established analytical methods and product inspections to provide consumer safety.<sup>1</sup> Especially for unregistered products, adulteration with chemical compounds remains a problem in China and other countries.

### NON HERBAL TCM

Uncertainty of and concern for hepatotoxicity exists also related to the use of non-herbal TCM elements.<sup>15,17,18,25,48,91,114-118</sup> They are commonly consumed together with herbal TCM products<sup>15,91</sup> and occasionally even named identically.<sup>91</sup> Known or potentially hepatotoxic non-herbal TCM elements are Bai Hua She (venom of the Chinese viper *Agris-trodon acutus*),<sup>15</sup> Jiang Can (dried larvae of *Bombyx Batryticatus*, infected by *Batrystis bassiana*),<sup>15</sup> Ling Yang Qing Fei (antelope horn),<sup>15</sup> Liyu Danzhi (carp juice),<sup>114</sup> Quan Xie (dry polypides of the scorpion *Butthus martensii*),<sup>15</sup> Sang Hwang (*Phellinus lihneus*, mushroom),<sup>17,18</sup> Song Rong (*Agaricus blazei*, Himematsutake as Japanese Kampo Medicine, mushroom),<sup>115</sup> Wu Gong (dried polypites of the centipede *Scolopendra subspinipes mutilans*),<sup>15</sup> Wu Shao She (syn. Wu Xiao She, Sheng Wu Shao She, parts of the snake *Zaocys dhumnades*),<sup>15</sup> and Yu Dan (fish gallbladder).<sup>116-118</sup> Details of their adverse properties to date often remain unexplored for some products.

### COCHRANE

The Cochrane Handbook provides some general recommendations related to adverse effects, especially choosing which adverse effects to include, the types of studies, and search methods for adverse effects.<sup>119</sup> These specifications do not necessarily apply to our short analysis, since we focused only on one single adverse effect and did not choose other adverse types. Our report also was based on single case reports or short case series, not on various types of detailed studies which actually are not available in the scientific literature for further assessment by us and others. Finally, specific search methods for hepatotoxicity cases have already been applied in this analysis, and there is no need for additional refinement.

However, the Cochrane Handbook<sup>119</sup> was a good basis evaluating and summarizing evidence from the Cochrane Collaboration for traditional Chinese medicine therapies with focus on herbal TCM.<sup>120</sup> Overall, 70 Cochrane systematic reviews of TCM were identified, including 42 reviews related to herbal TCM, with 22/42 herbal medicine reviews that concluded that there was not enough good quality trial evidence to make any conclusion about the efficacy of the evaluated treatment, while the remaining 20 herbal TCM reviews indicated a suggestion of benefit, which was qualified by a caveat about the poor quality and quantity of studies. Most reviews included many distinct interventions, controls, outcomes, and populations, and a large number of different comparisons were made, each with a distinct forest plot.<sup>120</sup>

Considering these uncertainties of therapeutic efficacy as summarized by the Cochrane reviews for herbal TCM<sup>120</sup> and the hepatotoxicity risk of herbal TCM use as outlined in the present study (Table 1), the risk/benefit/ratio is clearly negative.

### LIMITATION OF THE ANALYSIS

Products of herbal TCM commonly are used as TCM dietary supplements or TCM drugs. Product variability and lack of product standardization regarding their ingredients may create uncertainty and scientific discussions. In addition, listed herbs or products might be arguable as having merely a low affinity to TCM. For many TCM mixtures, only the primary pharmacologically active the other component, called the king herb, is mentioned as ingredient,<sup>6</sup> neglecting the other ingredients. This may

cause some irritation and discussion due to incomplete product specification.

## CONCLUSIONS

Liver injury was reported for 57 different TCM herbs and herbal mixtures. Causality was likely or probable for 28 out of these 57 herbal products based on the CIOMS scale, positive reexposure test results, or both, while the remaining cases often remained unassessable. Thus, further efforts are needed to enhance the quality of causality assessment for future cases of suspected herbal hepatotoxicity by TCM; an objective approach like the CIOMS scale should be applied in all cases.

## ACKNOWLEDGEMENT

The authors declare that they have no conflict on interest.

## REFERENCES

- Zhang L, Yan J, Liu X, Ye Z, Yang X, Meyboom R, Chan K, et al. Pharmacovigilance practice and risk control of Traditional Chinese Medicine drugs in China: Current status and future perspective. *J Ethnopharmacol* 2012; 140: 519-25.
- Tang JL, Liu BY, Ma KW. Traditional Chinese medicine. *Lancet* 2008; 372: 1938-40.
- NIH, National Center for Complementary and Alternative Medicine (NCCAM). Traditional Chinese Medicine: An Introduction. Last updated October 2013. Available at: <http://nccam.nih.gov/health/whatiscam/chinesemed.htm> [Accessed 7 July, 2014].
- National Institutes of Health (NIH) and LiverTox: Chinese and other Asian herbal medicines. Last updated 10 January 2013. Available at: <http://liver-tox.nih.gov/ChineseAndOtherAsianHerbalMedicines.htm> [Accessed 7 July, 2014].
- Ernst E. Review article. Methodological aspects of Traditional Chinese Medicine (TCM). *Ann Acad Med Singapore* 2006; 35: 773-4.
- Bunchohntavakul C, Reddy KR. Review article: herbal and dietary supplement hepatotoxicity. *Aliment Pharmacol Ther* 2013; 37: 3-17.
- Teschke R, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: A tabular compilation of reported cases. *Liver Int* 2012; 32: 1543-56.
- Teschke R, Schwarzenboeck A, Eickhoff A, Frenzel C, Wolff A, Schulze J. Clinical and causality assessment in herbal hepatotoxicity. *Expert Opin Drug Saf* 2013; 12: 330-66.
- Haller CA, Dyer JE, Ko R, Olson KR. Making a diagnosis of herbal-related toxic hepatitis. *West J Med* 2002; 176: 39-44.
- Estes JD, Stolpman D, Olyaei A, Corless CL, Ham JM, Schwartz JM, Orloff S. High prevalence of potentially hepatotoxic herbal supplement use in patients with fulminant hepatic failure. *Arch Surg* 2003; 138: 852-8.
- Talari P, Talari G, Gundareddy V, Vemula P, Barmeche J. Acute hepatitis associated with the chinese herbal product bai shi wan. Available at: [http://www.toothpicks.info/rc2/posters/2010/Internal\\_Medicine/Talari\\_P\\_Acute\\_hepatitis\\_associated.pdf](http://www.toothpicks.info/rc2/posters/2010/Internal_Medicine/Talari_P_Acute_hepatitis_associated.pdf) [Accessed 7 July, 2014].
- Perharic-Walton L, Murray V. Toxicity of traditional Chinese herbal remedies. *Lancet* 1992; 340: 674.
- Kane JA, Kane SP, Jain S. Hepatitis induced by traditional Chinese herbs: possible toxic components. *Gut* 1995; 36: 146-7.
- Vautier G, Spiller RC. Safety of complementary medicines should be monitored. *BMJ* 1995; 311: 633.
- Yuen MF, Tam S, Fung J, Wong DKH, Wong BCY, Lai CL. Traditional Chinese Medicine causing hepatotoxicity in patients with chronic hepatitis B infection: a 1-year prospective study. *Aliment Pharmacol Ther* 2006; 24: 1179-86.
- Jang JS, Seo EG, Han C, Chae HB, Kim SJ, Lee JD, Wang JH. Four cases of toxic liver injury associated with *Dictamnus dasycarpus*. *Korean J Hepatol* 2008; 14: 206-12 (Abstract in English, article in Korean).
- Kang SH, Kim JI, Jeong KH, Ko KH, Ko PG, Hwang SW, Kim EM, et al. Clinical characteristics of 159 cases of acute toxic hepatitis. *Korean J Hepatol* 2008; 14: 483-4 (Abstract in English, article in Korean).
- Sohn CH, Cha MI, Oh BJ, Yeo WH, Lee JH, Kim W, Lim KS. Liver transplantation for acute toxic hepatitis due to herbal medicines and preparations. *J Korean Soc Clin Toxicol* 2008; 6: 110-6 (Abstract in English, article in Korean).
- Cortez E, Boulger C, Bernard A. Ban Tu Wan hepatotoxicity. *BMJ Case Reports* 2012. DOI: 10.1136/bcr-2012-006438.
- Sangsuwan C, Udompanthurak S, Vannasaeng S, Thamlikitkul V. Randomized controlled trial of *Tinospora crispa* for additional therapy in patients with type 2 diabetes mellitus. *J Med Assoc Thai* 2004; 87: 543-6 (Abstract in English, article in Thai).
- Motoyama H, Enomoto M, Yasuda T, Fujii H, Kobayashi S, Iwai S, Morikawa H, et al. Drug-induced liver injury caused by a herbal medicine, bofu-tsutsu-sho-san. *Nihon Shokakibyo Gakkai Zasshi* 2008; 105: 1234-9 (Abstract in English, article in Japanese).
- Hwang SH, Park JA, Jang YS, Lee KM, Lee DS, Ahn BM, Lee EH. Case of acute cholestatic hepatitis caused by the seeds of *Psoralea corylifolia*. *Korean J Hepatol* 2001; 7: 341-4 (Abstract in English, article in Korean).
- Nam SW, Baek JT, Lee DS, Kang SB, Ahn BM, Chung KW. A case of acute cholestatic hepatitis associated with the seeds of *Psoralea corylifolia* (Boh-Gol-Zhee). *Clin Toxicol* 2005; 43: 589-91.
- Cheung WI, Tse ML, Ngan T, Lin J, Lee WK, Poon WT, Mak TW, et al. Liver injury associated with the use of *Fructus Psoraleae* (Bo-gol-zhee or Bu-gu-zhi) and its related property medicine. *Clin Toxicol* 2009; 47: 683-5.
- Chau TN. Drug-induced liver injury: an update. *Hong Kong Med Diary* 2008; 13: 23-6.
- Lee CH, Wang JD, Chen PC. Risk of liver injury associated with Chinese herbal products containing *Radix bupleuri* in 639,779 patients with hepatitis B virus infection. *PLoS ONE* 2011; 6(1): e16064. DOI: 10.1371/journal.pone.0016064
- Adachi M, Saito H, Kobayashi H, Horie Y, Kato S, Yoshioka M, Ishii H. Hepatic injury in 12 patients taking the herbal loss aids Chaso and Onshido. *Ann Intern Med* 2003; 139: 488-92.
- Lin TJ, Tsai MS, Chiou NM, Deng JF, Chiu NY. Hepatotoxicity caused by *Breynia officinalis*. *Vet Hum Toxicol* 2002; 44: 87-8.

29. Lin TJ, Su CC, Lan CK, Jiang DD, Tsai JL, Tsai MS. Acute poisonings with *Breynia officinalis* - an outbreak of hepatotoxicity. *J Toxicol Clin Toxicol* 2003; 41: 591-4.

30. Yoshida EM, McLean CA, Cheng ES, Blanc PD, Somberg KA, Ferrell LD, Lake JR. Chinese herbal medicine, fulminant hepatitis, and liver transplantation. *Am J Gastroenterol* 1996; 91: 2647-8.

31. Kamiyama T, Nouchi T, Kojima S, Murata N, Ikeda T, Sato C. Autoimmune hepatitis triggered by administration of an herbal medicine. *Am J Gastroenterol* 1997; 92: 703-4.

32. Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013; 144: 1419-25.

33. Verucchi G, Calza L, Attard L, Chiodo F. Acute hepatitis induced by traditional Chinese herbs used in the treatment of psoriasis. *J Gastroenterol Hepatol* 2002; 17: 1342-3.

34. Kim SY, Yim HJ, Ahn JH, Kim JH, Kim JN, Yoon I, Kim DI, et al. Two cases of toxic hepatitis caused by arrowroot juice. *Korean J Hepatol* 2009; 15: 504-9 (Abstract in English, article in Korean).

35. Bae SH, Kim DH, Bae YS, Lee KJ, Kim DW, Yoon JB, Hong JH, et al. Toxic hepatitis associated with *Polygoni multiflori*. *Korean J Hepatol* 2010; 16: 182-6 (Abstract in English, article in Korean).

36. Gono Y, Odaguchi H, Hayasaki T, Suzuki K, Oikawa T, Muranushi A, Akahoshi T, et al. Clinical analysis of cases with drug-induced liver injury for Kampo medicine. *Kampo Med* 2010; 61: 828-33 (Abstract in English, article in Japanese).

37. Linnebur SA, Rapacchietta OC, Vejar M. Hepatotoxicity associated with Chinese skullcap contained in Move Free Advanced dietary supplement: two case reports and review of the literature. *Pharmacotherapy* 2010; 750: 258e-262e.

38. Yang L, Aronsohn A, Hart J, Jensen D. Herbal hepatotoxicity from Chinese skullcap: A case report. *World J Hepatol* 2012; 4: 231-3.

39. Dhanasekaran R, Owens V, Sanchez W. Chinese skullcap in Move Free arthritis supplement causes drug induced liver injury and pulmonary infiltrates. *Case Reports Hepatol* 2013. Article ID 965092. DOI: org/10.1155/2013/965092.

40. Kang HS, Choi HS, Yun TJ, Lee KG, Seo YS, Yeon JE, Byun KS, et al. A case of acute cholestatic hepatitis induced by *Corydalis speciosa* Max. *Korean J Hepatol* 2009; 15: 517-23 (Abstract in English, article in Korean).

41. Jorge OA, Jorge AD. Hepatotoxicity associated with the ingestion of *Centella asiatica*. *Rev Esp Enferm Dig* 2005; 97: 115-24.

42. Kim YJ, Ryu SL, Shim JW, Kim DS, Shim JY, Park MS, Jung HL. A pediatric case of toxic hepatitis induced by *Hovenia dulcis*. *Pediatr Gastroenterol Hepatol Nutr* 2012; 15: 111-6.

43. Woolf GM, Petrovic LM, Rojter SE, Wainwright S, Villamil FG, Katkov WN, Michieletti P, et al. Acute hepatitis associated with the Chinese herbal product Jin Bu Huan. *Ann Intern Med* 1994; 121: 729-35.

44. Horowitz RS, Feldhaus K, Dart RC, Stermitz FR, Beck JJ. The clinical spectrum of Jin Bu Huan toxicity. *Arch Intern Med* 1996; 156: 899-903.

45. Picciotti A, Campo N, Brizzolara R, Giusto R, Guido G, Sinelli N, Lapertosa G, et al. Chronic hepatitis induced by Jin Bu Huan. *J Hepatol* 1998; 28: 165-7.

46. Divinsky M. Case report: Jin Bu Huan - not so benign herbal medicine. *Can Fam Physician* 2002; 48: 1640-2.

47. Inoue H, Yamazaki S, Shimizu M, Uozki H, Goto T, Ohnishi S, Koike K. Liver injury induced by the Japanese herbal drug kamishoyosan. *Gastroenterol Hepatol* 2011; 7: 692-5.

48. Garcia-Moran S, Saez-Rouuel F, Gento E, Lopez Morante A, Arias L. Acute hepatitis associated with *Camellia tea* and *Orthosiphon stamineus* ingestion. *Gastroenterol Hepatol* 2004; 27: 559-60.

49. Peyrin-Biroulet L, Petitpain N, Kalt P, Ancel D, Petit-Laurient F, Trechot P, Barraud H, et al. Probable hepatotoxicity from epigallocatecol gallate used for phytotherapy. *Gastroenterol Clin Biol* 2004; 28: 404-6 (Article in French).

50. Gloro R, Hourmand-Ollivier I, Mosquet B, Mosquet L, Rousselot P, Salamé E, Piquet MA, et al. Fulminant hepatitis during self-medication with hydroalcoholic extract of green tea. *Eur J Gastroenterol Hepatol* 2005; 17: 1135-7.

51. Javaid A, Bonkovsky HL. Hepatotoxicity due to extracts of Chinese green tea (*Camellia sinensis*): a growing concern. *J Hepatol* 2006; 45: 334-5.

52. Jimenez-Saenz M, Martinez-Sanchez M del C. Acute hepatitis associated with the use of green tea infusions. *J Hepatol* 2006; 44: 616-7.

53. Bonkovsky HL. Hepatotoxicity associated with supplements containing Chinese green tea (*Camellia sinensis*). *Ann Intern Med* 2006; 144: 68-71. Erratum in: *Ann Intern Med* 2006; 144: 380.

54. Molinari M, Watt KD, Kruszyna T, Nelson R, Walsh M, Huang WY, Nashan B, et al. Acute liver failure induced by green tea extracts: case reports and review of the literature. *Liver Transpl* 2006; 12: 1892-5.

55. Björnsson E, Olsson R. Serious adverse liver reactions associated with herbal weight loss supplements. *J Hepatol* 2007; 47: 295-7.

56. García-Cortés M, Borraz Y, Lucena MI, Peláez G, Salmerón J, Diago M, Martínez-Sierra MC, et al. Liver injury induced by "natural remedies": an analysis of cases submitted to the Spanish Liver Toxicity Registry. *Rev Esp Enferm Dig* 2008; 100: 688-95.

57. Sarma DN, Barrett ML, Chavez ML, Gardiner P, Ko R, Mähady GB, Marles RJ, et al. Safety of green tea extract: a systematic review by the US Pharmacopeia. *Drug Saf* 2008; 31: 469-84.

58. Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Rascagni R, Santuccio C, Mastrangelo S. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. *Eur J Clin Pharmacol* 2009; 65: 331-41.

59. Rohde J, Jacobsen C, Kromann-Andersen H. Toxic hepatitis triggered by green tea. *Ugeskr Laeger* 2011; 173: 205-206 (Abstract in English, article in Danish).

60. Navarro VJ, Bonkovsky HL, Hwang SI, Vega M, Barnhart H, Serrano J. Catechins in dietary supplements and hepatotoxicity. *Dig Dis Sci* 2013; 58: 2682-90.

61. Nadir A, Agrawal S, King PD, Marshall JB. Acute hepatitis associated with the use of a Chinese herbal product, ma-huang. *Am J Gastroenterol* 1996; 91: 1436-8.

62. Borum ML. Fulminant exacerbation of autoimmune hepatitis after the use of Ma Huang. *Am J Gastroenterol* 2001; 96: 1654-5.

63. Skoulios F, Alexander GJ, Davies SE. Ma huang associated acute liver failure requiring liver transplantation. *Eur J Gastroenterol Hepatol* 2005; 17: 581-4.

64. Reuben A, Koch DG, Lee WM, and the Acute Liver Failure Study Group. Drug-induced acute liver failure: Results of a U.S. multicenter, prospective study. *Hepatology* 2010; 52: 2065-76.

65. Culvenor CCJ, Edgar JA, Smith LW, Kumana CR, Lin HJ. *Heptotropium lasiocarpum* Fisch and Mey identified as cause of veno-occlusive disease due to herbal tea. *Lancet* 1986; 1(8487): 978.

66. Aiba T, Takahashi T, Suzuki K, Okoshi S, Nomoto M, Uno K, Aoyagi Y. Liver injury induced by a Japanese herbal medicine, sairei-to (TJ-114, Bupleurum and Hoelen combination, Chai-Ling-Tang). *J Gastroenterol Hepatol* 2007; 22: 762-3.

67. Tsuda T, Yashiro S, Gamo Y, Watanabe K, Hoshino T, Oikawa T, Hanawa T. Discrepancy between clinical course and drug-induced lymphocyte stimulation tests in a case of saireito-induced liver injury accompanied by Sjögren syndrome. *J Altern Complement Med* 2010; 16: 501-5.

68. Dai HF, Gao Y, Yang M, Yu CH, Gu ZY, Chen WX. Hepatic veno-occlusive disease induced by Gymura segetum: report of two cases. *Hepatobiliary Pancreat Dis Int* 2006; 5: 406-8.

69. Chen MY, Cai JT, Du Q. Hepatic veno-occlusive disease associated with the use of Gynura segetum. *Eur J Intern Med* 2007; 18: 609.

70. Li C, Liang XS, Li CZ. Sinusoidal obstruction syndrome associated with the ingestion of gynura root. *Clin Toxicol* 2010; 48: 962-4.

71. Lin G, Wang JY, Li N, Li M, Gao H, Ji Y, Zhang F, et al. Hepatic sinusoidal obstruction syndrome associated with consumption of Gynura segetum. *J Hepatol* 2011; 54: 666-73.

72. Gao H, Li N, Wang JY, Zhang SC, Lin G. Definitive diagnosis of hepatic sinusoidal obstruction syndrome induced by pyrrolizidine alkaloids. *J Dig Dis* 2012; 13: 33-9.

73. Cárdenas A, Restrepo JC, Sierra F, Correa G. Acute hepatitis due to shen-min: a herbal product derived from *Polygonum multiflorum*. *J Clin Gastroenterol* 2006; 40: 629-32.

74. But PPH, Tomlinson B, Lee KL. Hepatitis related to the Chinese medicine Shou-wu-pian manufactured from *Polygonum multiflorum*. *Vet Hum Toxicol* 1996; 38: 280-2.

75. Park GH, Mann SP, Ngu MC. Acute hepatitis induced by Shou-Wu-Pian, a herbal product derived from *Polygonum multiflorum*. *J Gastroenterol Hepatol* 2001; 16: 115-7.

76. Battinelli L, Daniele C, Mazzanti G, Mastrianni CM, Lichtenr M, Coletta S, Costantini S. New case of acute hepatitis following the consumption of Shou Wu Pian, a Chinese herbal product derived from *Polygonum multiflorum*. *Ann Intern Med* 2004; 140: 587-8.

77. Panis B, Wong DR, Hooymans PM, De Smet PAGM, Rosias PR. Recurrent toxic hepatitis in a Caucasian girl related to the use of Shou-Wu-Pian, a Chinese herbal preparation. *J Pediatr Gastroenterol Nutr* 2005; 41: 256-8.

78. Laird AR, Ramchandani N, deGoma EM, Avula B, Khan IA, Gesundheit N. Acute hepatitis associated with the use of an herbal supplement (*Polygonum multiflorum*) mimicking iron-overload syndrome. *Clin Gastroenterol* 2008; 42: 861-2.

79. Furukawa M, Kasajima S, Nakamura Y, Shouzushima M, Nagatani N, Takinishi A, Taguchi A, et al. Toxic hepatitis induced by Show-Wu-Pian, a Chinese herbal preparation. *Inter Med* 2010; 49: 1537-40.

80. Valente G, Sanges M, Campione S, Bellevicine C, De Francis G, Sollazzo R, Matera D, et al. Herbal hepatotoxicity: a case of difficult interpretation. *Eur Rev Med Pharmacol Sci* 2010; 14: 865-70.

81. Jung KA, Min HJ, Yoo SS, Kim HJ, Choi SN, Ha CY, Kim HJ, et al. Drug-induced liver injury: Twenty five cases of acute hepatitis following ingestion of *Polygonum multiflorum* Thun. *Gut Liver* 2011; 5: 493-9.

82. Banarova A, Koller T, Payer J. Toxic hepatitis induced by *Polygonum multiflorum*. *Vnitr Lek* 2012; 58: 958-62 (Abstract in English, article in Slovak).

83. Cohen SM, Heywood E, Pillai A, Ahn J. Hepatotoxicity associated with the use of White Flood, a nutritional supplement. *Practical Gastroenterology* 2012; October issue: 45-8.

84. Itoh S, Marutani K, Nishijima T, Matsuo S, Itabashi M. Liver injuries induced by herbal medicine, Syo-saiko-to (xiao-chai-hu-tang). *Dig Dis Sci* 1995; 40: 1845-8.

85. Hsu LM, Huang YS, Tsay SH, Chang FY, Lee SD. Acute hepatitis induced by Chinese hepatoprotective herb xiao-chai-hu-tang. *J Chin Med Assoc* 2006; 69: 86-8.

86. Teschke R. Traditional Chinese Medicine induced liver injury. *J Clin Translat Hepatol* 2014; 2: 80-94. DOI: 10.14218/JCTH.2014.00003.

87. Teschke R, Wolff A, Frenzel C, Schulze J. Review article: herbal hepatotoxicity - an update on traditional Chinese medicine preparations. *Aliment Pharmacol Ther* 2014; 40: 32-50.

88. Davies EG, Pollock I, Steel HM. Chinese herbs for eczema. *Lancet* 1990; 336: 117.

89. Graham-Brown R. Toxicity of Chinese herbal remedies. *Lancet* 1992; 340: 673.

90. Sanders D, Kennedy N, McKendrick MW. Monitoring the safety of herbal remedies: Herbal remedies have a heterogeneous nature. *Br Med J* 1995; 311: 1569.

91. Shaw D. Toxicological risks of Chinese herbs. *Planta Med* 2010; 76: 2012-8.

92. Pharmacopoeia of the People's Republic of China, Vol. 1. Beijing: Peoples Medical Publishing House; 2005.

93. Chan K. Chinese medicinal materials and their interface with Western medical concepts. *J Ethnopharmacol* 2005; 96: 1-18.

94. Danan G, Bénichou C. Causality assessment of adverse reactions to drugs - I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993; 46: 1323-30.

95. Teschke R, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: challenges and pitfalls of causality assessment methods. *World J Gastroenterol* 2013; 19: 2864-82.

96. Teschke R, Wolff A, Frenzel C, Schwarzenboeck A, Schulze J, Eickhoff A. Drug and herb induced liver injury: Council for International Organizations of Medical Sciences scale for causality assessment. *World J Hepatol* 2014; 6: 17-32.

97. Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, Hunt CM, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther* 2011; 89: 806-15.

98. National Institutes of Health (NIH) and LiverTox: Drug record. Ba Jiao Lian (Dysosma pleyanthum). Last updated 10 September 2013. Available at: <http://livertox.nih.gov/BaJiaoLian.htm> [Accessed 7 May, 2014].

99. Teschke R, Gentner A, Wolff A, Frenzel C, Schulze J, Eickhoff A. Herbal hepatotoxicity: Analysis of cases with initially reported positive reexposure tests. *Dig Liver Dis* 2014; 46: 264-9.

100. Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol* 1990; 11: 272-6.

101. Takikawa H. A proposal of the diagnostic scale of drug-induced liver injury. *Hepatology Res* 2005; 32: 250-1.

102. Chau TN, Cheung WI, Ngan T, Lin J, Lee KWS, Poon WT, Leung VKS, et al., and the Hong Kong Herb-Induced Liver Injury Network (HK-HILIN). Causality assessment of herb-induced liver injury using multidisciplinary approach and the Roussel Uclaf Causality Assessment Method (RUCAM). *Clin Toxicol* 2011; 49: 34-9.

103. Teschke R, Frenzel C, Schulze J, Schwarzenboeck A, Eickhoff A. Herbalife hepatotoxicity: Evaluation of cases with positive reexposure tests. *World J Hepatol* 2013; 5: 353-63.
104. Teschke R, Frenzel C, Glass X, Schulze J, Eickhoff A. Herbal hepatotoxicity: A critical review. *Br J Clin Pharmacol* 2013; 75: 630-6.
105. Teschke R, Lebot V. Proposal for a Kava Quality Standardization Code. *Food Chem Toxicol* 2011; 49: 2503-16.
106. Ernst E. Adulteration of Chinese herbal medicines with synthetic drugs: a systematic review. *J Intern Med* 2002; 252: 107-13.
107. Posadzki P, Watson L, Ernst E. Contamination and adulteration of herbal medicinal products (HMPs): an overview of systematic reviews. *Eur J Clin Pharmacol* 2013; 69: 295-307.
108. National Institutes of Health (NIH) and LiverTox: Drug record. Chi R Yun (*Bryonia officinalis*). Last updated 25 October 2013. Available at: <http://livertox.nih.gov/ChiRYun.htm> [Accessed 7 July, 2014].
109. Wu GL, Yu GY, Chen J. Clinical analysis of hepatic veno-occlusive disease induced by *Sedum aizoon*. *Zhongguo Zhong Yao Za Zhi* 2008; 33: 2402-4 (Abstract in English, article in Chinese).
110. Wang JY, Gao H. Tuscanqi and hepatic sinusoidal obstruction syndrome. *Dig Dis* 2014; 15: 105-7.
111. Kumana CR, Ng M, Lin HJ, Ko W, Wu PC, Todd D. Herbal tea induced hepatic veno-occlusive disease: quantification of toxic alkaloid exposure in adults. *Gut* 1985; 26: 101-4.
112. Kumana CR, Ng M, Lin HJ, Ko W, Wu PC, Todd D. Hepatic veno-occlusive disease due to toxic alkaloid in herbal tea. *Lancet* 1983; II: 1360-1.
113. Ko RJ. Adulterants in Asian patent medicines. *N Engl J Med* 1998; 339: 847.
114. Son HS, Kim GS, Lee SW, Kang SB, Back JT, Nam SW, Lee DS, et al. Toxic hepatitis associated with carp juice ingestion. *Korean J Hepatol* 2006; 12: 103-6 (Abstract in English, article in Korean).
115. Mukai H, Watanabe T, Ando M, Katsumata N. An alternative medicine, *Agaricus blazei*, may have induced severe hepatic dysfunction in cancer patients. *Jpn J Clin Oncol* 2006; 36: 808-10.
116. Chan DWS, Yeung CK, Chan MK. Acute renal failure after eating raw fish gall bladder. *BMJ* 1985; 295: 897.
117. Xuan BHN, Thi TXN, Nguyen ST, Goldfarb DS, Stokes MB, Rabenou RA. Ichthyotoxic ARF after fish gallbladder ingestion: a large case series from Vietnam. *Am J Kidney Dis* 2003; 41: 220-4.
118. Kung SW, Chan YC, Tse ML, Lau FL, Chau TL, Tam MKP. Acute renal failure and hepatitis following ingestion of carp gallbladder. *Clin Toxicol* 2008; 46: 753-7.
119. Higgins JPT, Green S (eds.). *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Book). Wiley Blackwell, Chichester, West Sussex, England; 2008.
120. Manheimer E, Wieland S, Kimbrough E, Cheng K, Berman BM. Evidence from the Cochrane Collaboration for traditional Chinese medicine therapies. *J Alternat Complement Med* 2009; 15: 1001-4.