



Literature review of liver injury induced by *Tinospora crispa* associated with two cases of acute fulminant hepatitis



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ABSTRACT

Introduction: Species of *Tinospora* are used as herbal remedies for the treatment of various diseases with very few toxic effects having been reported. *Tinospora cordifolia* (TCF) has been reported to effectively prevent hepatotoxicity. However, there are an increasing number of cases revealing that *Tinospora crispa* (TCP) might have the negative effect of inducing hepatotoxicity. Because of the similar leaves, people may mistake TCP for TCF, and consume it with the purpose of protecting liver function.

Objective: Find out the misusing level of TCP and TCF and which chemical compound in TCP might induce hepatotoxicity.

Methods: We report two cases of acute fulminant hepatitis associated with chronic use of TCP. Given that the two herbs were misidentified in these two reports, we investigated the frequency of erroneous identification by using three keywords (“Guduchi”, “*Tinospora cordifolia*”, “*Tinospora crispa*”) to search images from the Google Images database. To further clarify the influence of liver function between TCP and TCF, we searched PubMed (up to 29 July 2018) for relevant publications on clinical trials or case reports.

Results: Based on web review, over 35 percent of websites failed to accurately identify these two herbs. The different effects on liver function between TCP and TCF were compared through literature review. It indicated that TCF exerted liver protection, TCP had a contrary effect, suggesting its *cis*-Clerodane-type furano-diterpenoids might be an important factor of inducing hepatotoxicity.

Conclusions: We concluded that people might cause hepatic injury or even death without correctly identifying these two *Tinospora* species.

1. Introduction

Tinospora cordifolia (TCF) and *Tinospora crispa* (TCP) are both somewhat erroneously known as Guduchi in India.¹ The stem of *Tinospora cordifolia* is an herbaceous vine of the family Menispermaceae, indigenous to the tropical areas of India and Sri Lanka, and was recorded in Ayurvedic and Jamu. It is a folk medicine commonly used for

the treatments of joint pain, muscle strain, and lower back pain. Recent studies on TCF have shown that it has protective effects against both hepatotoxic and immunotoxin consequences from carbon tetrachloride (CCl₄) intoxication, and it also inhibits hepatocellular carcinoma (HCC), induced by diethylnitrosamine (DEN).^{2,3} TCF has furthermore been reported to effectively prevent hepatotoxicity induced by anti-tubercular drugs, not only in rats but also in humans.⁴ The possible

Abbreviations: ACP, acidic phosphatase; AKT, protein kinase B; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAT, catalase; CCl₄, carbon tetrachloride; CT, controlled trial; DBL, direct bilirubin; DEN, diethylnitrosamine; ED, emergency department; GSH, glutathione; GST, GSH S-transferase; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HDLC, HDL cholesterol; LDL, low-density lipoprotein; RCT, randomized controlled trial; SOD, superoxide dismutase; T2DM, diabetes mellitus type 2; TBL, total bilirubin; TCF, *Tinospora cordifolia*; TCP, *Tinospora crispa*; TG, Triglyceride; γ -GT, gamma-glutamyltransferase

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mechanisms by which TCF protects against chemotoxicity and carcinogenicity, could be due to improvement of Kupffer cell function⁵ and preservation and/or enhancement of antioxidative enzymes (GSH S-transferase (GST), catalase (CAT) and superoxide dismutase (SOD)) in the liver.⁶

Tinospora crispa (L.) Hook. f. & Thomson, called K'u T'eng (苦藤) or Po Yeh Ch'ing Niu Tan (波葉青牛膽) in Chinese, is an herbaceous vine which grows extensively in the tropical and subtropical regions of Southeast Asia. The decoction from the stem of TCP is used to inhibit inflammation, decrease thirst, enhance hunger, and cool down body temperature as an antipyretic in order to maintain good health.⁷ However, there are an increasing number of cases revealing that TCP might have the negative effect of inducing hepatotoxicity.^{8,9} Because of the similar leaves, people may mistake TCP for TCF, and consume it with the purpose of protecting liver function. It may have a high risk of activating hepatotoxicity. Herein we report two cases of acute fulminant hepatitis induced by TCP.

2. Material and methods

2.1. Case reports

In November of 2007, a 63-year-old man without chronic hepatitis B or C virus infection was admitted to our emergency department (ED) suffering from altered mental status after having consumed the juice of the TCP stem for one week. Levels of hepatic enzymes and bilirubin were both elevated (AST/ALT: > 2000/ > 2000 U/L, TBL: > 20) (Table 1). After admission to the hospital, the patient continued to consume the TCP juice, despite strictly being asked to stop. Ten days after the initial hospital admission, the patient's clinical conditions progressed, however the patient discharged himself against medical advice. The patient subsequently died in the middle of November 2007.

Another case was reported in May 2009, when a 57-year-old man was admitted to the ED having suffered from upper-right abdominal discomfort, yellowish skin appearance, and icteric sclera for the previous two weeks. He had a history of chronic hepatitis C virus infection, alcoholism, and hepatocellular carcinoma, with regular follow up. He started to drink the juice of the stem of an unidentified plant before admission. He consumed 100 ml of the juice every day beginning in the middle of April 2009. A laboratory examination was performed in the ED, showing AST 5322 U/L, ALT 1844 U/L, and TBL 10 mg/dl (Table 1). Blood urea nitrogen and serum creatinine were within normal range. After admission, this unknown plant was brought to the hospital and we were consulted for further identification and authentication. Suspecting it to be one of the *Tinospora* genus, we sent the original plant to the Chinese medicine pharmacy department for further identification, which confirmed it to be TCP. Written informed consents were obtained in print form from the family of the deceased patient and from the patient in order for publication of these two cases.

2.2. Web review

Given that the two herbs were misidentified in these two reports, we aimed to investigate the frequency of erroneous identification by using three keywords ("Guduchi", "*Tinospora cordifolia*", "*Tinospora crispa*") to search images from the Google Images database.

Table 1
Liver function of 2 patients.

	Patient #1 in 2007				Patient #2 in 2009				
	Late Oct.	4, Nov	7, Nov	14, Nov.	20, Mar.	7, May.	15, May.	1, Jun.	3, Aug.
AST (U/L)	> 2000	466	227	61	75	5322	1918	202	59
ALT (U/L)	> 2000	923	414	57	88	1844	682	67	32
TBL (mg/dL)	> 20	25.3	35	31.8	0.8	10	18.6	22.4	9.6

First, we used Google search engine to search three keywords from 2018/7/28 - 7/29. Second, we only involved the websites which have images. Third, we excluded the websites which are repeated, unable to enter or other search engines. Fourth, we excluded the websites which images don't contain the stem or are not clear. Fifth, we identified the stems of plant whether they are prominently blunt or not (Fig. 1). The stem of TCF, a climbing shrub, glabrous, succulent, often reaching a great height and sending down long thread-like aerial roots, is not apparently prominent blunt. On the other hand, the stem of TCP is climbing and twining, however strongly blunt (Fig. 1). Therefore, even TCF and TCP present very similar leaves (Fig. 1), they can be easily distinguished by their stems. Sixth, we differentiated the websites to be commercial if the websites are selling products, or academic if the websites are teaching the knowledge. The flow chart of search method is shown in Supplementary Fig. 1, and the additional data are demonstrated in Supplementary Data.

2.3. Literature review

To further clarify the influence of liver function between TCP and TCF, we searched PubMed (up to 29 July 2018) for relevant publications on clinical trials or case reports using combinations of the following keywords: 'Guduchi', '*Tinospora cordifolia*', '*Tinospora crispa*', 'liver toxicity', 'hepatotoxicity', 'hepatic effect' and 'acute hepatitis'. We recruited 16 literary articles, which excluded multiple herbal formulations. In regard to TCP, there are 1 randomized controlled trial (RCT), 2 controlled trials (CT) and 2 case reports involved and there are 11 CTs related to TCF.

3. Results and discussion

These two cases demonstrated that the liver injury and death were associated with TCP. The first patient's liver function deteriorated in parallel with severe jaundice after continuing to intake TCP. The second patient's liver function improved gradually after cessation of TCP consumption; eventually, the first patient died, while the second patient survived. These two cases indicate that TCP stem juice exhibits hepatotoxicity in patients with and without chronic liver diseases. Many patients believe that phytomedicines are inherently safe for consumption, and generally do not consider the potential pharmacological interactions between botanical and conventional medicines.

Moreover, in our web review, the search results of the keywords "Guduchi", and "*Tinospora cordifolia*" both disclosed that over 35 percent of images with blunt stems are actually prominent (Table 2). It may misguide people to identify the TCP to TCF, especially the commercial websites (87% and 80%). In addition, it implied that these commercial websites might potentially use the wrong origins. The search results of the keyword "*Tinospora crispa*" showed 96 percent with prominent blunt stems (Table 2). It indicated that merchants, herbalists, and even some scholars may mistakenly identify TCP as TCF. Because of the misguiding from lots of websites, especially the commercial ones, they will fail to accurately identify the herbs leading to erroneously consumption of TCP juice to induce liver toxicity instead of consuming TCF for liver protection.

TCP is sourced mostly from Southeast Asian countries, including Thailand, Malaysia, and Vietnam^{8,9,12} while TCF is sourced mostly from



Fig. 1. Photos of *Tinospora cordifolia* (A)¹⁰ and *Tinospora crispa* (B) (Filmed by Ching-Yeh Tu). Illustrations of *Tinospora cordifolia* (C) and *Tinospora crispa* (D)¹¹.

Table 2
Search results of three keywords.

Keyword “Guduchi”			
Not prominent blunt stems		Prominent blunt stems	
72(62%)		39(35%)	
Commercial	Academic	Commercial	Academic
34(47%)	38(53%)	34(87%)	5(13%)
Keyword “ <i>Tinospora cordifolia</i> ”			
Not prominent blunt stems		Prominent blunt stems	
131(66%)		69(35%)	
Commercial	Academic	Commercial	Academic
50(38%)	81(62%)	55(80%)	14(20%)
Keyword “ <i>Tinospora crispa</i> ”			
Not prominent blunt stems		Prominent blunt stems	
5(4%)		136(96%)	
Commercial	Academic	Commercial	Academic
0(0%)	5(100%)	90(66%)	46(34%)

India.^{13–20} While the stems of both herbs are used in treatments, other plant parts of TCF, including the aerial roots, leaves, and roots are also consumed (Table 3). The dosage forms of TCP are powders, pellets, and extracts by ethanol or methanol; meanwhile, the dosage forms of TCF are powders, isolated crystal, and the extracts by ethanol, pet ether, water, sediment, or grind juice (Table 3). In terms of usage for human, there is no significant difference of dosage used between these two herbs. The average duration of TCP use is approximately 2 ~ 6 months^{8,21} longer than the 14 days of TCF’s consumption.¹⁷

Animal model studies of TCP consumption have demonstrated

significantly higher levels of cholesterol, lower levels of blood glucose, and reduced body weight. However, a high dosage or long-term use of TCP will induce increases of liver enzyme levels, including ALP, ALT, γ -GT, and bilirubin, both in human and rat model studies.^{12,22} These levels will return to normal after discontinuation of TCP, similar to the case discussed in the present report. The pathological changes to liver induced by TCP both in humans and rats demonstrated significantly higher incidence of bile duct proliferation, hepatocytes degeneration, centrilobular necrosis of hepatocytes associated with inflammatory cell infiltration containing lymphocytes and mononuclear cells.^{8,9,12,21,22} As for TCF, it demonstrated significant liver-protective effects by reducing elevated liver enzymes and reversing liver tissue damage to near normal.^{2,3,13–20}

As reported, 65 chemical compounds have been identified in TCP⁷ 9 of which belong to *cis*-Clrodane-type furano-diterpenoids.^{23,24} Furan is a heterocyclic organic compound, consisting of a five-membered aromatic ring with four carbon atoms and one oxygen atom, and is formed during commercial or domestic thermal treatment of food. Chemical compounds containing such rings are also referred to as furans. Studies have shown that exposure to furan at dosage of approximately 2000 times higher than normal increases the risk of hepatocellular tumors in rats and mice, and bile duct tumors in rats. Therefore, furan is classified as a potential human carcinogen.²⁵ Other herbal remedies containing furan, such as *Dioscorea bulbifera*, containing furano-norditerpenoids²⁶ or *Teucrium chamaedrys*, containing furano-diterpenoids^{27–30} have also been shown to induce hepatotoxicity. As reported,³¹ dosages of 2 ~ 4 mg/Kg of furan may induce cholangiocarcinoma in rats, and hepatocellular carcinoma in mice. TCP contains approximately 1.875 mg/kg of the chemical groups of *cis*-Clrodane-type furano-diterpenoids²³

Table 3
Literature survey on hepatic effect by TCP and TCF.

Reference	Design	Models/Patients (Total sample size)	Duration of treatment	Comparison group(s) (n)	Outcome measurement	Effect
<i>Tinospora crispa</i> Chavalitumrong et al. (1997) ²²	CT	16 Wistar rats of each sex (80)	1.28 g ethanol stem extract/kg bw/day for 6 months	Water (16) Trageacanth (16)	Liver weight Hematological study Blood chemistry study	Significantly higher incidence of bile duct proliferation and focal liver cell hyperplasia in male groups. Significantly higher levels of cholesterol, higher ALP, ALT and relative liver weights
Sangsuwan et al. (2004) ²¹	RCT	20 patients with T2DM (40)	3 g powder in capsule form/day for 6 months	Placebo (20)	Blood chemistry study	2 patients with higher levels of liver enzymes returning to normal after discontinuing TCP.
Denis et al. (2007) ⁸	Case report	1 woman (1)	720 mg stem powder/day for 10 weeks		Blood chemistry study	Most patients with significant cholesterol elevation. Hepatic cytolysis (transaminases AST: 13 N and ALT: 18 N) and cholestasis (γ -GT: 4 N). Normalization of the transaminases obtained after stopping treatment for 6 weeks.
Kadir et al. (2011) ¹²	CT	10 male Sprague Dawley rats (50)	100 and 200 mg ethanol stem extract/kg- bw/day for 8 weeks	Normal (8) Normal saline (10) TAA (12)	Liver weight Hematological study Blood chemistry study	Significantly lower serum albumin. Significantly higher liver body weight and serum activities of ALT, AST, ALP, bilirubin and γ -GT levels. Hepatocytes degeneration, centrilobular necrosis of hepatocytes. Inflammatory cell infiltration containing lymphocytes and mononuclear cells. AST: 1.169 IU/l, ALT: 2.029 IU/l, TBL: 20.47 mg/dl, DBL: 13.29 mg/dl, and γ -GT: 243 IU/l. Centrilobular necrosis with inflammatory cell infiltration compatible with a toxic etiology. Complete recovery after discontinuation.
Langrand et al. (2014) ⁹	Case report	1 man (1)	10 pellets/day for 4 weeks		Hematological study Blood chemistry study Histology	Significantly less half-life of carbon clearance
<i>Tinospora coriifolia</i> Nagarkatti et al. (1994) ⁵	CT	8 rats with horse-serum intoxication (24)	100 mg stem powder/kg bw/day for 4 weeks	Normal (8) Horse-serum (8)	Kupffer cell activity	Significant reduction in serum levels of AST, ALT, ALP, bilirubin
Bishayi et al. (2002) ³²	CT	4 male Wistar rats with CCl4 intoxication (16)	100 mg stem extract/kg bw/day for 15 days	Normal (4) CCl4 (4)	Blood chemistry study	Significantly less levels of liver enzymes.
Adhvaryu et al. (2007) ¹³	CT	4 Duncan Hartley guinea pigs with AKT intoxication (40)	200 mg aerial root powder/kg bw/day for 21 days	TCF only (4) Normal (4) AKT (4)	Histology Blood chemistry study	Significantly higher level of antioxidants and detoxification enzymes. Significantly lower levels of transaminase level. Hepatic marker enzymes were near normal. Remarkably reduced tumor incidence and reversed damaged hepatocytes to normal status. Increasing activities of SOD and CAT. Decreasing levels of AST, ALT, ALP, and ACP enzymes.
Dhanasekaran et al. (2009) ³	CT	10 male Wistar rats with DEN induced liver tumor (50)	10 mg stem isolated crystal /kg bw/day for 20 weeks and last 12 weeks	Normal (10) DEN (10) TCF only (10)	Blood chemistry study Tumor incidence	Significantly higher levels of liver enzymes.
Sharma and Pandey (2010) ¹⁴	CT	6 male Swiss rats with lead intoxication (36)	400 mg stem and leaf extract/kg bw/day for 30 days	Normal (6) Lead (6) TCF stem only (6) TCF leaf only (6)	Blood chemistry study Histology	Significantly lower levels of TBL, ALT, AST and ALP.
Kavitha et al. (2011) ¹⁵	CT	6 Wistar rats with CCl4 intoxication (72)	200 mg stem, leaf and root extract (ether, ethanol and water)/kg bw/day for 3 days	Normal (6) CCl4 (6) CCl4 + Silymarin (6) Normal (6) DEN (6)	Lead estimation Histopathology Blood chemistry study Blood chemistry study	Lower levels of enzymatic and non-enzymatic antioxidants values.
Jayaprakash et al. (2015) ¹⁶	CT	6 male Wistar rats with DEN induced liver tumor (24)	300 mg whole plant extract/kg bw/day for 30 days	TCF only (6) DEN (14) Normal (14)	Blood chemistry study Histology	Significant lower levels of γ -GT, AST, ALT, TG, Cholesterol, HDL and LDL. Significantly lower levels of ALT, AST.
Sharma and Dabur (2016) ¹⁷	CT	12 asymptomatic moderate alcoholics without chronic liver disease (26)	100 ml (3.0 g stem extract)/day for 14 days	Normal (10)	Blood chemistry	
Alsuhaibani and Khan (2017) ¹⁸	CT	10 BALB/C mice with Salmonella intoxication (70)	100, 200, 500 mg stem extract (water and ethanol)/kg bw/day for 7 days	Normal (10)	Blood chemistry	

(continued on next page)

Table 3 (continued)

Reference	Design	Models/Patients (Total sample size)	Duration of treatment	Comparison group(s) (n)	Outcome measurement	Effect
Chavan et al. (2017) ¹⁹	CT	6 male Wistar rats with alcohol intoxication (36)	200 mg extract (water and sediment)/kg bw/day for 15 days	Normal (6) Alcohol (6) Alcohol + Silymarin (6)	Blood chemistry Histology	Significant improvements in the total protein content, the liver function tests and the lipid profile tests except for HDLC. Significantly lower levels of lipid peroxidation and GSH. The liver histology showed improvements despite the collection of many lymphocytes within the hepatic parenchyma and the prominent Kupfer cells.
Kaushik et al. (2017) ²⁰	CT	6 Swiss rats with plant extract administered for 7 days and paracetamol intoxication on 8 th day (42)	200 mg stem extract (grind juice and water)/kg bw/day for 7 days	Normal (6) Paracetamol (6) Paracetamol + Liv-52 (6)	Blood chemistry Histology	Both extracts significantly decreased the elevated enzyme levels to normal level and are equally potent in the inhibition of free radical generation.

Note: TCP = *Tinospora crispa*; TCF = *Tinospora cordifolia*; CT = controlled trial; RCT = randomized controlled trial; ALP = alkaline phosphatase; ALT = alanine aminotransferase; T2DM = Diabetes mellitus type 2; AST = aspartate aminotransferase; γ -GT = gamma-glutamyl transferase; TBL = total bilirubin; CCl4 = carbon tetrachloride; AKT = protein kinase B; DEN = diethyl nitrosamine; SOD = superoxide dismutase; CAT = catalase; ACP = acidic phosphatase; TG = Triglyceride; HDL = high-density lipoprotein; LDL = low-density lipoprotein; HDLC = HDL cholesterol; GSH = Glutathione.

further indicating that long-term consumption of TCP may potentially cause liver damage.

4. Conclusions

The evidence from reports and pertinent literature suggest that TCP has the potential to induce hepatotoxicity and even fatal consequence in patients with or without chronic liver diseases. Therefore, persistent use of high doses of TCP should be avoided, and if any signs of hepatotoxicity occur while using herbal medicine possibly containing TCP, consumption of the drug should be ceased immediately. Furthermore, the web review disclosed that many websites might demonstrate erroneous images between TCP and TCF. Health care workers and herbalists need to be aware of the high rates of misidentification, and be responsible for informing and educating patients or general people of the potential hazards of traditional herbal medicines potentially containing TCP.

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Authors' contributions

WTH wrote the draft and contributed to create tables. CYT and FYW identified the plants and created figures. STH designed, conceived the study and amended the manuscript. WTH, CYT, FYW and STH approved the final manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

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