Review Article

Herb-induced liver injury (HILI) with 12,068 worldwide cases published with causality assessments by Roussel Uclaf Causality Assessment Method (RUCAM): an overview

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Abstract: Herbal products including herbal medicines are worldwide used in large amounts for treating minor ailments and for disease prevention. However, efficacy of most herbal products has rarely been well documented through randomized controlled trials in line with evidence-based medicine concepts, which could be used to estimate the benefit/risk ratio. Instead, much better documented are adverse reactions such as liver injury associated with the consumption of some herbal products, so called herb-induced liver injury (HILI), which represents a clinical challenge. In order to establish HILI as valid diagnosis, the use of a diagnostic algorithms such as Roussel Uclaf Causality Assessment Method (RUCAM) is widely recommended, although physicians in some countries are reluctant to use RUCAM for their HILI cases. This review on worldwide HILI and RUCAM, developed as part of the artificial intelligence ideas, reveals that China is the leading country with 24 publications on HILI cases that were all assessed for causality using RUCAM, followed by Korea with 15 reports, Germany with 9 reports, the US with 7 reports, and Spain with 6 reports, whereas the remaining countries provided less than 4 reports. The total number of assessed HILI cases is 12,068 worldwide derived from 80 publications but in each report HILI case numbers were variable in a range from 1 up to 6,971. This figure compares with 46,266 cases of drug-induced liver injury (DILI) published worldwide from 2014 to early 2019 also assessed for causality by RUCAM. The original version of RUCAM was validated and established in 1993 and updated in 2016 that should be used in future HILI cases. RUCAM is an objective, structured, and validated method, specifically designed for liver injury. It is a scoring system including case data elements to be assessed and scored individually to provide a final score in five causality gradings. Among the 11,404/12,068 HILI (94.5%) cases assessable for evaluation, causality gradings were highly probable in 4.2%, probable in 15.5%, possible in 70.3%, and unlikely or excluded in 10.0%. To improve the future reporting of RUCAM based HILI cases, recommendations include the strict adherence to instructions outlined in the updated RUCAM and, in particular, to follow prospective data collection on the cases to ensure completeness of case data. In conclusion, RUCAM can well be used to assess causality in suspected HILI cases, and additional efforts are now required to increase the quality of the reported cases.

Keywords: Liver injury; drug-induced liver injury (DILI); herb-induced liver injury (HILI); Roussel Uclaf Causality Assessment Method (RUCAM)

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Introduction

Herb-induced liver injury (HILI) is a rare adverse reaction associated with the consumption of herbal products like herbal medicines or more specifically regulatory approved herbal drugs and presents clinical features similar to those of drug-induced liver injury (DILI) (1-3). Validated specific biomarkers are not commonly available to diagnose either HILI, perhaps with the exception of a few herbs (4), or DILI (5) with the required degree of likelihood. It is therefore necessary to use a strong and reliable causality assessment method (CAM) such as RUCAM (Roussel Uclaf Causality Assessment Method) to diagnose liver injury (1-6). The original RUCAM was validated and established in 1993 (7,8) with an update in 2016 (9).

A substantial variability was observed among countries whenever liver injury cases had been evaluated using published data (6,10). Their common analytical basis was the use of RUCAM in liver injury cases. However, a systematic worldwide analysis of liver injury cases based on causality assessment by RUCAM was restricted so far to DILI in a study of 46,266 cases presented as case reports or case series published from 2014 to early 2019 (6). No such systematic evaluation of RUCAM based HILI cases worldwide focusing on countries is available.

This analysis presents for the first time an overview on the international literature with focus on the worldwide use RUCAM in HILI cases and critically evaluates the quality of the published reports with respect to completeness of case data and the proportion of highly probable and probable causality gradings. The case evaluation was extended to lower gradings with the most likely alternative cause. Finally, the extent of published reports of HILI cases not assessed for causality using RUCAM was evaluated and compared with well assessed HILI cases showing high causality gradings.

Literature search and source

The PubMed database was used to identify publications for the following terms: Herb induced liver injury; Herbal medicine; Herbal traditional medicine; HILI; Traditional Chinese medicines; TCM; RUCAM; Roussel Uclaf Causality Assessment Method. Search terms were used either alone or combined with other terms. Articles in English were preferred and checked for the suitability to be included in the review article. This excluded, for instance, reports from China published in Chinese language but allowed inclusion of Chinese reports published in English language journals with transparent data accessible for peer review. Search period ended on 14 March 2020.

Definitions

Only herbs causing HILI were considered, which include a variety of herbal products and more specifically herbal traditional medicines with herbal traditional Chinese medicines (TCMs) or traditional occidental medicines (TOM) in general, and regulatory approved herbal drugs. This definition excludes *a priori* any of the so called herbal dietary supplements (HDS) from the present analysis.

Countries with RUCAM based HILI cases, RUCAM specificities, and HILI epidemiology

Countries worldwide and regions

Scientists from countries throughout the world including regions of Asia, Europe, North America, South America, South Africa, and Australia published HILI cases after assessment for causality using RUCAM (*Table 1*), referencing in particular in alphabetical order to reports from Australia (11,12), Austria (13), Brazil (14), China with reports from 2006 until 2019 (15-36), China with more recent reports of 2020 (37,38), and Colombia (39), France (40), Germany (41-49), India (50,51), Italy (52-54), and Japan (55,56), followed by Korea (57-71), Singapore (72,73), South Africa (74), Spain (75-80), Sweden (81), Switzerland (82), Turkey (83), and finally the US (84-91).

The current analysis of scientists favoring the use of RUCAM showed that China is on top with 24 publications on RUCAM based HILI cases, followed by Korea with 15 reports, Germany with 9 reports, the US with 7 reports, and Spain with 6 reports, whereas the remaining countries provided less than 3 reports. Among the reports, the number of HILI cases may vary from 1 to 6,971. Considering all RUCAM based cases, the total number of 12,068 HILI cases worldwide includes 443 cases from non-Asian countries versus 11,625 cases from Asian countries. Therefore, non-Asian countries contributed with 3.7% to the worldwide cases as opposed to Asian countries with 96.3%. This difference could be partly due to the known high herbal consumption in Asian countries as compared with non-Asian countries but the exact data of herbal consumption is unknown.

Table 1 Worldwide countries with a selection of published HILI cases assessed for causality using RUCAM, occasionally reported together with DILI cases

Country/HILI cases [n]	Author	Year	HILI [n], DILI [n]	Products	Comments
Australia [2]	Smith (11)	2016	HILI [1]	*Garcinia Cambogia*	With RUCAM a core of 6 was reported, which corresponds to a probable causality grading
	Laube (12)	2019	HILI [1]	Ginseng	Using the updated RUCAM, a score of 7 was achieved and thereby a probable causality grading
Austria [2]	Stadlbauer (13)	2005	HILI [2]	Various herbs contained in Tahitian NONI juice	RUCAM use provided with a score of 7 a probable causality grading in one case and with a score of 5 a possible causality grading in the other case
Brazil [1]	Barcelos (14)	2019	HILI [1]	*Senecio brasiliensis*	The updated RUCAM provided with a score of 6 a probable causality grading
China [10,993]	Yuen (15)	2006	HILI [7]	Several herbs	Using RUCAM for causality assessment, gradings were highly probable (not definitive!) in 3 patients, probable in 2 cases, and possible in 2 patients
	Cheung (16)	2009	HILI [3]	*Psoralea corylifolia*	RUCAM based causality assessment provided with scores of 6–8 in all cases a probable causality grading
	Chau (17)	2011	HILI [27]	Multiple herbs	With RUCAM, causality gradings were highly probable in 5 cases, probable in 16, possible in 5, and unlikely in 1 case
	Lin (18)	2011	HILI [1]	*Gynura segetum*	Using the original RUCAM, a score of 6 corresponding to a probable causality grading was reported
	Gao (19)	2012	HILI [5]	*Gynura segetum*	The original RUCAM provided a score of 5 in 2 cases, of 6 in 1 case, and of 7 in 2 cases, corresponding to possible or probable causality gradings
	Lai (20)	2012	HILI [74], DILI [64]	Multiple herbs and drugs	With RUCAM, scores were ≥6 in line with a probable or highly probable causality grading
	Dong (21)	2014	HILI [18]	*Polygonum multiflorum*	RUCAM provided 4× a probable and 14× a highly probable causality grading
	Hao (22)	2014	HILI [87], DILI [13]	Multiple herbs and drugs	RUCAM was used to assess causality whereby a subgroup of HILI or DILI cases with a score of ≥3 (possible or higher) were included
	Gao (23)	2015	HILI [23]	PA containing herbs	RUCAM was used, cases with a score of >5 were included (causality grading of probable, score: 5.52±0.67)
	Ou (24)	2015	HILI [130], DILI [361]	Multiple herbs and drugs	Unspecified RUCAM, not clearly quoted version was used for HILI, providing a probable or highly probable causality grading
	Wang (25)	2015	HILI [40]	*Polygonum multiflorum*	Use of RUCAM, and within a subgroup: 9× highly probable, 15× probable, and 16× possible causality gradings
	Zhu (26)	2015	HILI [158]	*Polygonum multiflorum*	The original RUCAM was used with a score of ≥3 for the included cases
	Zhang (27)	2016	HILI [54]	Multiple herbs	Use of the updated RUCAM provided a highly probable causality grading in 26 cases and a probable one in 28 cases
	Zhu (28)	2016	HILI [866], DILI [870], both [552]	Multiple herbs and drugs	RUCAM was used for the large cohorts consisting of HILI, DILI, or both, and causality gradings were highly probable in 320 HILI cases, probable in 504 cases, possible in 41 cases, and excluded in one case. In many HILI cases, a large list of comedications by drugs is recognized as confounders

Table 1 *(continued)*

Table 1 *(continued)*

Country/HILI cases [n]	Author	Year	HILI [n], DILI [n]	Products	Comments
	Li (29)	2017	HILI [1]	*Polygonum multiflorum*	By using the updated RUCAM, reported causality grading was probable
	Chow (30)	2019	HILI [1,552]	Many single herbs [1,428] or mixtures with multiple herbs [124]	RUCAM based causality gradings were: probable or higher for 138 cases of HILI by single herbs and for 56 cases by herbal mixtures; possible for 226 cases of HILI by single herbs and for 27 cases by herbal mixtures; but lacking causality for 1,064 cases of HILI by single herbs and for 41 cases by herbal mixtures
	Jing (31)	2019	HILI [145]	*Polygonum multiflorum*	With the updated RUCAM, causality gradings were highly probable in 16 cases, probable in 120 cases, and possible in 9 cases
	Li (32)	2019	HILI [1]	*Polygonum multiflorum*	The updated RUCAM was used, but not specifically referenced, providing a score of 10 as a highly probable causality grading
	Liu (33)	2019	HILI [331]	*Polygonum multiflorum*	RUCAM was used but without providing causality gradings
	Shen (34)	2019	HILI [6,971], DILI [18,956]	Multiple herbs and drugs	RUCAM based assessment with scores ≥3 in all HILI cases but causality grading was not differentiated from additional, RUCAM based 18,956 DILI cases
	Tan (35)	2019	HILI [3]	*Swietenia macrophylla*	RUCAM score was 7 in all 3 patients, in line with a probable causality grading
	Zhu (36)	2019	HILI [488]	Multiple herbs	Using the updated RUCAM, causality grading was highly probable in 52 cases (10.5%), probable in 370 cases (74.8%), and possible in 66 cases (13.3%)
	Gao (37)	2020	HILI [1]	*Psoralea*	RUCAM based causality grading was possible due to a score of 3
	Xia (38)	2020	HILI [7]	*Swietenia macrophylla*, syn. skyfruit	With the updated RUCAM, causality scores were 1×10 and thereby highly probable, and 2×8 and 4×7 and thereby probable
Colombia [1]	Cárdenas (39)	2006	HILI [1]	*Polygomun multiflorum*	Using RUCAM, a probable causality grading was achieved
France [10]	Parlati (40)	2017	HILI [10]	*Aloe vera*	With RUCAM, causality was probable in 8 cases and highly probable in 2 cases
Germany [160]	Teschke (41)	2009	HILI [1]	Ayurveda herbs	RUCAM provided with a score of 8 a probable causality for *Psoralea corylifolia*, contained in Bakuchi, the highest scored causality grading among the 4 different herbs that were used concomitantly, and with a score of 6 again a probable but lower scored causality for *Acacia catechu*, contained in Khadin, for *Eclipta alba* or *Bacopa monnieri*, contained in Brahmi, and for *Vetivexia zizaniodis*, contained in Usheer
	Teschke (42)	2011	HILI [22]	*Chelidonium majus* syn. Greater Celande	With RUCAM use, causality for *Chelidonium majus* was highly probable in 2 cases, probable in 6, possible in 10, unlikely in 1 case, and excluded in 3 cases
	Teschke (43)	2012	HILI [21]	*Chelidonium majus* syn. Greater Celandine	Using RUCAM, causality gradings for *Chelidonium majus* were highly probable in 2 cases, probable in 6, possible in 10, and excluded in 3 cases

Table 1 *(continued)*

Table 1 *(continued)*

Country/HILI cases [n]	Author	Year	HILI [n], DILI [n]	Products	Comments
	Douros (44)	2016	HILI [10], DILI [188]	Various herbs	RUCAM was used, and the resulting causality gradings were possible or probable
	Teschke (45)	2015	HILI [12]	*Camellia sinensis,* syn. Green tea, or Lu Cha	RUCAM provided a highly probable causality for Camellia sinensis in 5 patients, a probable causality in 6 patients, and a possible one in 1 patient
	Melchart (46)	2017	HILI [26]	Herbal TCMs	Using the updated RUCAM, causality was probable in 8 cases, possible in 16, and excluded in 2 cases
	Anderson (47)	2019	HILI [48]	*Petasites hybridus*	RUCAM was used in all cases together with the WHO global introspection method, not allowing clear identification of RUCAM based causality gradings
	Gerhardt (48)	2019	HILI [1]	*Chelidonium majus,* syn. Greater Celandine	RUCAM was used, which provided a score of 9 and thereby a causality of highly probable (the mentioned definite one is not a RUCAM term). The RUCAM source remained unquoted, and the used special criteria for the reexposure test remained also undisclosed
	Teschke (49)	2019	HILI [19]	*Camellia sinensis*	RUCAM based causality assessments presented 8 cases with a probable and 11 patients with a possible causality grading
India [111]	Philips (50)	2018	HILI [94]	Ayurvedic and other herbs	With RUCAM, causality gradings for 33 cases were possible, probable, or highly probable (definite as mentioned is not a RUCAM term), the other cases received not any RUCAM based causality grading; data are vaguely presented, cohorts were not uniform but mixed and therefore difficult to be characterized
	Philips (51)	2019	HILI [17]	Various herbs	RUCAM based causality gradings were possible or probable
Italy [75]	Lapi (52)	2010	HILI [1]	*Serenoa repens*	With RUCAM use, a probable causality was reported
	Mazzanti (53)	2015	HILI [19]	*Camellia sinensis*, syn. green tea	Using RUCAM, causality gradings were probable in 8 cases and possible in 11 cases
	Mazzanti (54)	2017	HILI [55]	*Red yeast rice*	RUCAM provided causality gradings of highly probable in 1 case, probable in 31 cases, possible in 18, unlikely in 3, and unassessable in 2 cases; for 7 cases among this cohort, a positive reexposure was mentioned but specific criteria used for the statement were not provided and also not referenced
Japan [3]	Tsuda (55)	2010	HILI [1]	Saireito	The use of the original RUCAM of 1993 provided a RUCAM score of 8 and thereby a probable causality grading
	Hisamochi (56)	2013	HILI [2]	*Agaricus blazei Murill*	With the RUCAM of 1993, a score of 6 and thereby a probable causality grading for both cases was achieved
Korea [493]	Ahn (57)	2004	HILI [64]	Various herbs	Use of RUCAM with modifications by the authors, providing mostly probable and highly probable causality gradings
	Seo (58)	2006	HILI [17]	Various herbs	RUCAM was used, and cases with a score of at least 3 were included
	Kang (59)	2008	HILI [66], DILI [38]	Various herbs and drugs	RUCAM provided scores ≥4 for all HILI cases corresponding to a possible grading or higher
	Sohn (60)	2008	HILI [24]	Various herbs	RUCAM was applied in all HILI patients undergoing a liver transplantation

Table 1 *(continued)*

Table 1 *(continued)*

Country/HILI cases [n]	Author	Year	HILI [n], DILI [n]	Products	Comments
	Kang (61)	2009	HILI [1]	*Corydalis speciosa*	Reported was the use of a RUCAM version, but modified by the authors, providing a score of 9 and thereby a highly probable causality grading
	Kim (62)	2009	HILI [2]	Arrowroot, syn. Ge Gen	The use of RUCAM provided a score of 10 and thereby a highly probable causality grading
	Bae (63)	2010	HILI [1]	*Polygonum multiflorum*	With RUCAM, a final score of 10 was achieved corresponding to a highly probable causality grading
	Yang (64)	2010	HILI [3]	*Aloe vera* or *arborescens*	RUCAM based scores of 7 in 2 cases provided a probable causality grading, and a score of 9 was achieved in the third patient corresponding to a highly probable causality grading (a definitive one as erroneously stated in the text does not exist in the RUCAM system)
	Jung (65)	2011	HLI [25]	*Polygonum multiflorum*	With RUCAM, the scores were 6–8 corresponding to a probable causality grading in 15 patients and were >9 corresponding to a highly probable causality grading in 10 patients
	Kim (66)	2012	HILI [1]	*Hovenia dulcis,* syn. Jugulu	Using RUCAM, a score of 6 was obtained for this case corresponding to a probable causality grading
	Suk (67)	2012	HILI [149], DILI [101], HILI [27]	Various herbs and drugs	RUCAM based evaluation for HILI cases provided an average score of 7 with a range of 3–12 and thereby a possible, probable, or highly probable causality grading
	Lee (68)	2015	HILI [97]	Various herbs	Use of a modified RUCAM, lack of any quotation and of causality grading
	Lee (69)	2015	HILI [5]	Various herbs	Using RUCAM, scores were 8.2±1.4, individual cases received mostly a highly probable or probable causality grading
	Woo (70)	2015	HILI [5]	Various herbs	A simplified RUCAM was used that provided probable causality gradings
	Cho (71)	2017	HILI [6]	Various herbs	RUCAM was used without specification of its version and referencing, providing a probable causality grading in 4 HILI cases and a possible grading in 2 cases
Singapore [25]	Wai (72)	2006	HILI [15], DILI [14]	Various herbs and drugs	RUCAM was used in HILI patients for causality assessment, but individual causality gradings were not reported. It was mentioned that all cases fulfilled all RUCAM criteria collected in the course of a prospective study, which suggests a causality grading of at least probable due to the expected data completeness
	Teo (73)	2016	HILI [10]	Various herbs	RUCAM was used in 10 assessable cases, with scores from 0 to 2 in 9 patients and a score of 5 in 1 patient
South Africa [47]	Awortwe (74)	2018	HILI [47]	Various herbs	Using the updated RUCAM, causality gradings were highly probable in 4 cases, probable in 27 cases, possible in 15 cases, and excluded in 1 case
Spain [47]	Andrade (75)	2005	HILI [9], DILI [452]	Various herbs	RUCAM was used but no specification of causality gradings was provided
	Jimenez-Saenz (76)	2006	HILI [1]	*Camellia sinensis*	Using RUCAM but without quoting the respective reference, causality for *Camellia sinensis* was highly probable (score 9), but criteria used for the positive reexposure test were not provided
	García-Cortés (77)	2008	HILI [13]	Various herbs	With RUCAM, causality in 7 cases was probable, and in 6 cases highly probable (by authors erroneously classified as definite, a term not used by RUCAM)

Table 1 *(continued)*

Table 1 *(continued)*

Country/HILI cases [n]	Author	Year	HILI [n], DILI [n]	Products	Comments
	García-Cortes (78)	2008	HILI [5]	Various herbs	With RUCAM assessed but causality gradings were not published for the evaluated cases
	Sáez-González (79)	2016	HILI [1]	Chelidonium majus	RUCAM was used and provided a score of 5 and thereby a possible causality grading
	Medina-Caliz (80)	2018	HILI [18]	*Camellia sinensis* and other herbs	Using RUCAM, causality gradings were highly probable in 1 case, probable in 13 cases, and possible in 4 cases
Sweden [5]	Björnsson (81)	2007	HILI [5]	*Camellia sinensis*	Using RUCAM, individual scores were from 6 up to 9, signifying probable or highly probable causality gradings
Switzerland [1]	Ruperti-Repilado (82)	2019	HILI [1]	*Artemisia annua*	Using the updated RUCAM, a score of 6 was achieved and thereby a probable causality grading
Turkey [1]	Yilmaz (83)	2015	HILI [1]	Lesser Celandine, syn. Pilewort	Application of RUCAM provided a score of 7 in line with a probable causality grading
United States [91]	Papafragkakis (84)	2016	HILI [1]	Chinese skullcap plus Black catechu	With the updated RUCAM, for the herbal mixture a score of 8 was achieved corresponding to a probable causality grading
	Kesavarapu (85)	2017	HILI [1]	Multiple herb	Use of a not correctly quoted RUCAM provided a score of 6 and thereby a probable causality grading
	Kothadia (86)	2018	HILI [19]	*Garcinia Cambogia*	With the updated RUCAM, scores of 7 and 8 were obtained corresponding to a probable causality grading for all cases
	Surapaneni (87)	2018	HILI [19]	*Camellia sinensis*	RUCAM based score was 5 in line with a possible causality grading, but the source of the used RUCAM was not quoted
	Imam (88)	2019	HILI [1]	Curcumin	Using the updated RUCAM, a score of 6 was obtained and thereby a probable causality grading
	Osborne (89)	2019	HILI [1]	*Mitragyna speciosa,* syn. Kraton	RUCAM assessment provided a score of 6 and thereby a probable causality grading
	Oketch-Rabah, USP (90)	2020	HILI [29]	*Camellia sinensis* extract	Using RUCAM likely as in the updated version, scores of ≥6 were achieved in line with a probable or highly probable causality grading but individually scored case numbers were not provided
	Schimmel (91)	2020	HILI [20]	*Mitragyna speciosa*, syn. Kraton	Using the updated RUCAM, causality gradings were unlikely in 3 cases, possible in 13, and probable in 4 cases

The above comments refer to RUCAM based HILI cases only, excluding DILI cases. Part of this table was published before (10) and has now been expanded substantially. DILI, drug-induced liver injury; HILI, herb-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method, TCM, traditional Chinese medicines; USP, United States Pharmacopeia; WHO, World Health Organizations.

HILI assessed for causality by RUCAM

For the majority of the listed HILI reports (*Table 1*), the original RUCAM of 1993 was used, with providing the accurate reference (7,8), but recent publications applied more frequently the updated RUCAM, first available since 2016 (9). In addition, other patients with clinically assumed HILI have likely been assessed for causality using RUCAM in a private practice or clinical setting without submitting these cases to publications. These unquantifiable cases would subsequently increase the number of the listed cases (*Table 1*). Occasionally, another CAM was used in addition to RUCAM, conditions that might disturb results of causality gradings and prevent comparison with HILI cohorts using RUCAM alone.

In a few reports, the highest causality grading for HILI was erroneously reported as certain or definite (*Table 1*); none of these terms are used in RUCAM publications (7-9) as any biological result including those of a human disease cannot be classified higher as highly probable, there is nothing certain or definite in any biological setting.

Causality gradings and case data quality

The variability of RUCAM based causality gradings is of interest (*Table 1*) and merits further comments (*Table 2*). From the initially published 12,068 HILI cases, only 11,404 cases (94.5%) contained sufficient data on RUCAM based causality gradings (*Table 2*). Consequently, in 5.5% of the cases causality gradings were not provided although RUCAM was applied in these cases. Regrettably, this omission invalidates the conclusions proposed in these case reports of this small HILI subgroup and represents waste of time, financials, and energy of scientists, editors, and reviewers. In more detail, based on 11,404 assessable HILI cases, causality gradings were highly probable in 4.2% of the cases, probable in 15.5% of the cases, possible in 70.3% of the cases, and other gradings like unlikely or excluded in 10.0% of the cases (*Table 2*). Unquestionable, HILI cases best qualified for further case characterization regarding specific herbs are those with a highly probable or a probable causality grading, both represent 19.7% of the assessable cases (*Table 2*). High causality gradings were commonly achieved under the following conditions: first, data are derived from studies with a prospective design, allowing for straight forward collection of data sets and their completeness; second, single cases were assessed prospectively, asking for all RUCAM based specific elements in advance at time of first suspected diagnosis

Table 2 Worldwide countries with a selection of published HILI cases assessed for causality using RUCAM providing various causality gradings

Country	Assessable cases/ initial cases/% [n/n/%]	Highly probable [n/%]	Probable [n/%]	Possible [n/%]	Other grades [n/%]	Comments
All countries worldwide	11,404/12,068 94.5%	487/4.2%	1,765/15.5%	8,016/70.3%	1,136/10.0%	Out of 12,068 published RUCAM based HILI cases, 11,404 cases (94.5%) were assessable for causality grading
Australia	2/2/100%	-	2/100%	-	-	Low case numbers but all cases received a high causality grading of probable and benefitted from this classification
Austria	2/2/100%	-	1/50%	1/50%	-	One case was provided with a causality grading of probable
Brazil	1/1/100%	–	1/100%	–	–	In this single case, perfect and appreciated causality grading of probable
China	10,663/10,993/97.0%	447/4.2%	1,497/14.0%	7,611/71.4%	1,108/10.4%	Valuable are the 1,944 HILI cases with a highly probable or probable causality grading, but associated with 1,108 cases with an unlikely or excluded causality grading
Colombia	1/1/100%	–	1/100%	–	–	Perfect causality grading in this single case
France	10/10/100%	2/20%	8/8%	–	–	Appreciated high causality gradings of highly probable and probable

Table 2 *(continued)*

Table 2 *(continued)*

Country	Assessable cases/ initial cases/% [n/n/%]	Highly probable [n/%]	Probable [n/%]	Possible [n/%]	Other grades [n/%]	Comments
Germany	111/112/99.1%	10/9.0%	35/31.5%	57/51.4%	9/8.1%	Virtually all published cases (99.1%) provided causality gradings, but high case numbers with a possible or lower causality gradings
India	50/111/45.0%	–	–	50/100%	–	All cases reached only a possible causality grading
Italy	75/75/100%	1/1.3%	40/53.3%	29/38.7%	5/6.7%	Many HILI cases with a probable causality grading as compared with lower cases numbers of causality gradings of possible
Japan	3/3/100%	–	3/100%	–	–	Small case numbers but with causality gradings of probable
Korea	300/493/60.9%	14/4.7%	52/17.3%	234/78.0%	–	Among the published 439 cases, only 60.9% provided causality gradings including extremely high case numbers (n=234) with an unlikely or excluded causality grading
Singapore	25/25/100%	–	15/60%	1/4.0%	9/36.0%	All 25 cases provided a causality grading including a probable grading in 15 cases
South Africa	47/47/100%	4/8.5%	27/57.5%	15/31.9%	1/2.1%	All published HILI cases were assessable regarding causality grading with higher case numbers [31] providing a highly probable and probable grading compared with 15 cases presenting a possible one
Spain	33/47/70.2%	8/24.2%	20/60.6%	5/15.2%	–	Out of 47 published HILI case, 33 cases were assessable for causality grading, providing 28 cases with a highly probable and probable grading as opposed to 5 cases with a possible grading
Sweden	5/5/100%	–	5/100%	–	–	Excellent study, all cases were assessable and provided a probable causality ranking
Switzer-Land	1/1/100%	–	1/100%	–	–	Perfect single case report with a probable causality grading
Turkey	1/1/100%	–	1/100%	–	–	Single case report, fulfilling with a causality grading of probable all requirements for a good case evaluation
United States	74/91/81.3%	–	56/75.7%	13/17.6%	4/5.4%	Out of published 91 HILI cases, 74 cases (81.3%) were assessable for causality grading and presented 57 cases with a highly probable and probable grading as opposed to 13 cases with a less desired possible grading

Listed are for each country the causality gradings with HILI case numbers and in percentages calculated from assessable cases of the respective country. Occasionally, published reports presented scores ≥6 that would include causality gradings of probable and highly probable, for reasons of clarity and homogeneity, all these cases were included in the lower grading category of probable. Similarly, all cases with a score ≥3 or ≥4 were included in the possible causality category, and cases with a score ranging from 3 to 12 were incorporated in the possible causality grading group. Data are derived from Table1 that provides additional details. HILI, herb-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method.

and ensuring complete data and high gradings upon final evaluation; third, cases with causality not meeting highly probable or probable gradings may have been deleted prior to publication to provide cohort homogeneity. In line with these considerations, HILI cases with possible causality gradings are mostly the result of insufficient data, obtained from retrospective studies or single cases. It has repetitively and strongly been proposed that RUCAM works best in a prospective setting of data collection to ensure complete data with chances of high causality gradings (6-9,92-95). Of note, among the assessable cases and based on case numbers, best values for highly probable causality gradings were provided in China with 447 cases representing 4.2% of all assessable cases in this country (*Table 2*).

RUCAM specificities

RUCAM with its favored specificities has seemingly a good run worldwide as evidenced by assessing causality in 46,266 DILI cases (6) and now confirmed in 12,068 HILI cases (*Table 1*), with many details and proposals ensuring its correct application, providing appropriate case data quality and allowing for high causality gradings (6-9,92-95). For DILI, a RUCAM-DILI Case Quality (RDCQ) system has been proposed (6) that can be translated into HILI as well because many essentials apply to both DILI and HILI. RUCAM is objective, structured, validated, quantitative, transparent, user friendly, and specifically designed for liver injury by assessing liver specific elements, for which individual scores are attributed (9). Authors used RUCAM smoothly in their 12,068 HILI cases (*Table 1*) and 46,266 DILI cases (6). Problems were not reported, confirming its user-friendly use (9).

Summing up the individual element scores of RUCAM provides a final score and resulting causality grading: score ≤0, excluded causality; 1–2, unlikely; 3–5, possible; 6–8, probable; ≥9, highly probable (9). For future HILI case characterization, only cases with probable or highly probable causality gradings should be included in study cohorts. The updated RUCAM should be the preferred version with all its specificities to be used in future cases of both HILI and DILI (9). The aim of RUCAM is to clearly specify causality gradings using scores of assessed key elements rather than applying obscure percentages of causality ranges, leaving room for arbitrary modifications as known from the recent study from China and the US that published causality upgrading from possible to probable gradings likely in order to increase the power of conclusions (34). In addition, and as confirmed in court for another US study, intentional uptonings of RUCAM scores from possible to probable gradings invalidate published conclusions as outlined in detail (96,97) and recently (10), disregarding ethics commonly prevailing within the scientific community (6).

Actually and in retrospect, RUCAM is now to be seen as part of the recently promoted artificial intelligence (AI) ideas which calls for using algorithms to prevent arbitrary opinions, concepts early recognized already at the time of the introduction of RUCAM in the DILI and HILI community in 1993 (7,8). In fact, RUCAM is an objective diagnostic algorithm that overcomes previous attempts of causality assessment by the vague and subjective global introspection (GI) approach (94,95). GI is not liver specific, not structured, and not based on specific elements to be scored individually, and there is good evidence that RUCAM outperforms any other CAM, which are still caught up in the pre-RUCAM and pre-AI era and thereby neglecting the use of preferred diagnostic algorithms. It is said that most of these CAMs will not survive the next years unless all RUCAM specificities are incorporated one by one into the other CAMs.

As an important specificity, RUCAM was the first CAM that ever recognized the importance of various types of liver injury for a robust causality assessment (7-9). Based on thorough case analyses, three types of liver injury pattern emerged that showed striking differences of their clinical features and courses, with focus on challenge, dechallenge, and reexposure characteristics (9). Using results from laboratory analyses of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) and not from liver histology, these three types were classified as hepatocellular injury, cholestatic liver injury, and mixed liver injury. Due to the variability of their clinical features, specific key items and individual scores had to be defined for each of the three liver injury types. Subsequent analyses led to the conclusion that for the causality assessment, only two instead of three RUCAM versions are necessary, one for the hepatocellular injury and the other one for the cholestatic liver injury and the mixed liver injury with its predominant cholestatic features, with details outlined earlier (9). Types of liver injury were randomly mentioned in the HILI reports under consideration (*Table 1*).

In line with recommendations presented in the updated RUCAM, liver injury is defined by increased serum activities of liver tests (LTs) with the following thresholds (9): ALT of at least 5× upper limit of normal (ULN) and/or

of ALP of at least 2× ULN provided ALP is of hepatic origin, both best assessed simultaneously on the day of first presentation of suspected liver as outlined in 2016 (9). In the original RUCAM of 1993, ALT thresholds of 2× ULN were lower (7,8) but these values should not be applied anymore to ensure exclusion of cases reflecting unspecific, clinically not relevant liver injury, liver adaptation, more frequent cause of liver injury such as nonalcoholic steatohepatitis (NASH), or simple LT abnormality. In the current analysis, some HILI reports were assessed with low threshold values (*Table 1*), which increased the total number of suspected HILI cases. The current ALT and ALP threshold values of 2016 (9) are also considered as relevant in China (98). For sake of comparability, in future publications of HILI, these thresholds should be used and mentioned in the method section. In fact, actual threshold information is often lacking in HILI publications (*Table 1*).

Another specificity of RUCAM is the optional rather than mandatory inclusion of results from unintentional reexposure tests, but prerequisite for case inclusion is the application of strict criteria before and during reexposures (9). In detail, to classify a reexposure test as positive, criteria are required. For the hepatocellular injury, ALT levels before reexposure (designated as baseline ALT or ALTb) and reexposure ALT levels (designated as ALTr). The reexposure test is positive if ALTb is <5× ULN and ALTr is ≥2× ALTb, negative if one or both criteria are not fulfilled, and uninterpretable if data are lacking for one or both criteria. For the cholestatic or the mixed liver injury, the criteria and interpretation of results are similar, with ALT replaced by ALP (9). A positive reexposure test result is a hallmark of DILI and HILI and recognized by a maximum achievable score of 3 in RUCAM (9). Clearly, reexposure test is unintentional since intentional test is unethical due to high risks of severe outcome of liver injury. Results of reexposure tests using defined criteria have rarely been reported in the HILI cases under consideration (*Table 1*). However, high causality gradings in HILI are easily achievable without the need of these tests. In other studies, claimed positive reexposure test results from reexposures have rarely been confirmed following reassessment due to absence of strict criteria (99,100). For instance, among 34 HILI cases with initially reported positive reexposure tests, 61.8% of the cases actually fulfilled established test criteria, with negative tests in 17.6% and uninterpretable tests in 20.6% of the cases (100).

RUCAM considers alternative causes in a transparent approach (9). This is needed because many published HILI cases are not true HILI but such cases have to be attributed to alternative causes (101). Cohorts with inclusion of true HILI cases and liver diseases unrelated to herbal use but due to alternative causes lead inevitably to wrong descriptions of HILI features and conclusions. DILI cohorts show also flaws in the assessment of alternative causes (102,103).

Simultaneous use of RUCAM with other CAMs reported in few cases (*Table 1*) should be discouraged because it clouds the results of causality gradings. Modification of RUCAM also mentioned in a few publications (*Table 1*) should also be discouraged because the changes have not been validated. Clearly, RUCAM assesses causality for the herbal product *in toto* and cannot differentiate between the toxicity of the phytochemicals or the components willingly added to the products such as chemical drugs as adulterants or accidently contaminated by impurities, heavy metals, or toxins.

Obviously, RUCAM is unable to replace methods of herb authentication, an important issue as in some HILI cases where the used herbs had been misidentified. RUCAM also has no extra key element for quality issues of the herbal product (9), resulting from batch to batch variability, plant circadian clock system, biotic or abiotic plant stress, seasonal variation, or non-optimum area of harvest (104).

Cohorts of HILI and DILI

Opposed to European reports, Asian reports often and regretfully included a mix of HILI and DILI cases (*Table 1*), conditions not facilitating a characterization of HILI features resulting in high confusion in the offending products (*Table 3*). This analysis extends the previously one of HILI and DILI cases that were not based on RUCAM (105). In future studies a clear separation of HILI cases from DILI cases is indispensable. Difficult to reconcile is also the tendency to identify liver injury by herbs as DILI rather than correctly as HILI as outlined in some reports (*Table 1*). This may lead to confusion. Consequently and by definition, herbs cause HILI and not DILI, and HILI cases cannot be subsumed under the DILI cases.

In Asian countries analyzing the ratio of HILI to DILI (*Table 1*) provides variable results, best explained by differences in the primary study design favoring either HILI or DILI (*Table 3*). In European countries, however, RUCAM based HILI cases prevail over RUCAM based DILI cases (*Table 3*). Clearly, the number of reports is small, but both HILI and DILI cases were drawn from the same ethnic population allowing for a more robust comparison.

Table 3 Selected countries with published HILI cases assessed for causality using RUCAM, reported together with RUCAM based DILI cases

Region	Country	Author	Year	HILI [n], DILI [n]	HILI/DILI ratio
Asia	China	Lai (20)	2012	HILI [74], DILI [64]	1.16
		Hao (22)	2014	HILI [87], DILI [13]	6.7
		Ou (24)	2015	HILI [130], DILI [361]	0.36
		Zhu (28)	2016	HILI [563], DILI [870]	0.65
		Shen (34)	2019	HILI [6,971], DILI [18,956]	0.37
	Korea	Kang (59)	2008	HILI [66], DILI [38]	1.74
		Suk (67)	2012	HILI [149], DILI [101]	1.48
	Singapore	Wai (72)	2006	HILI [5], DILI [14]	0.36
Europe	Germany	Douros (44)	2016	HILI [10], DILI [188]	0.05
	Spain	Andrade (75)	2005	HILI [9], DILI [452]	0.02

HILI, herb-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method; DILI, drug-induced liver injury.

On a worldwide base, the 12,068 HILI cases (*Table 1*) are substantially lower as compared with the reported 46,266 DILI cases (6). However, this divergence should not lead to the erroneous conclusion that risks of liver injury are much higher for patients using conventional drugs than those consuming herbal medicines because the population exposed to each product category is unknown.

HILI epidemiology

Best data of HILI epidemiology can be achieved using a prospective study design that ensures completeness of case data, whereby all cases should be assessed for causality using the updated RUCAM including LT thresholds and causality gradings of probable and highly probable.

Valid data on HILI epidemiology have rarely been reported and are available for a few countries only, but some critical issues remain (34,46,68,71). For instance, a low HILI prevalence was found in a large retrospective single center study from Korea in 27/4,769 patients (0.6%) with musculoskeletal disorders receiving TCMs (68), with confirmed results through a thorough reevaluation as published by the same group (106). In Korea again, HILI prevalence has been reported from a nationwide multicenter and prospective study with 6/1,001patients (0.6%) (71). These results from one single country as presented by two different groups are surprising and require comments. With 0.6%, identical data of HILI prevalence were achieved (68,71,106), although one group used a retrospective design commonly known for its low case quality (68,106), whereas the other group followed a prospective study design (71). The case definition in both groups using HILI cases was ALT thresholds of at least 3× ULN (68,71,106). With higher ALT threshold of ≥5× ULN, HILI case numbers approached the zero range (71). HILI epidemiology is seemingly not a problem in Korea (68,71,106), a situation similar to Germany considering low TCM-related HILI incidence data (46). In the latter report, liver injury data were collected from a prospective, hospital-based and large-scale study of 21,470 patients who had no liver disease prior to treatment with herbal TCM. Among these, 26 patients (0.12%) experienced HILI defined as ALT values of ≥5× ULN but causality as assessed by the updated RUCAM (9) was probable in only 8 cases, possible in 16 patients and excluded in 2 cases (46).

In China with around 1.4 billion inhabitants, HILI epidemiology is more complex (34,107). In particular, valid epidemiology data of HILI are not available for the population although herbal TCMs are constituents of the Chinese health system. An earlier disputable epidemiology analysis was not RUCAM based and used mixed cohorts of liver injury by drugs, herbs, or complementary and alternative medicines (106). Instead, improvements brought were evident in a recent report focusing on incidence and etiology of DILI in mainland China, which in fact considered both HILI and DILI (34). It was now recognized that the use of RUCAM as a valuable diagnostic algorithm can help assess causality in liver injury cases (34). However, the cohorts still included under the term of DILI not only DILI but also liver injury cases caused by herbal TCM

and HDS, again presenting the shortcomings of the earlier study (106), not allowing for characterization of HILI epidemiology features (34). Nevertheless, some progress is recognizable because other critical shortcomings have been well identified in the text under the limitation section (34). A new version of this study is promised and will hopefully be published with inclusion of the updated RUCAM of 2016, then without major flaws and after a careful peer review preventing letters to the editor. With the current data and methods, no valid statement is reasonable on HILI epidemiology in China (34). Nevertheless, China is well prepared to present valid data on HILI cases, all assessed by RUCAM to distinguish incidence from prevalence, considering major differences in definitions as outlined earlier (10).

RUCAM based HILI cases without confirmed causality

There are few HILI cohorts with cases, which lost their initially claimed causality after reassessment with RUCAM (*Table 4*) (108-112). These cohorts share the common feature of being initially submitted as spontaneous reports to regulatory agencies or governmental institutes, which inappropriately handled the causality assessment of these cases (108). Shortcomings included the failure to initiate a formal and robust causality assessment approach or the use of diagnostic methods that were not validated for liver injury preventing any firm conclusion. However and in spite of these methodological issues, some regulatory agencies including the one in Germany announced a restricted market availability for a previously authorized herbal drug because of the risk of liver injury. Despite formal request, the German regulatory agency BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) refused access to anonymized case data in order to reassess the cases with RUCAM. However, anonymized case details were readily obtained from the involved manufacturers. Assessments with RUCAM showed insufficient data quality and many confounders such as preexisting liver disease or comedication, leading then to the conclusion that the initially claimed HILI was not substantiated. Finally, via a recent court decision against the German regulatory ban of kava (*Piper methysticum*) and in support of case analyses mainly from the group of the first author (R Teschke), the controversy has now hopefully been settled. According to a comprehensive report published 2015, the administrative court of Cologne in Germany ruled that the available data do not support the alleged liver injury of kava, the herbal anxiolytic drug and traditional herb in Oceania (113). Overall, the number of cases seemed insignificant for the court when compared with the known exposure data of 450 million daily doses in ten years. As the German regulatory agency came under scientific fire, it removed its statements of 2002 from its internet home page, but the file has been preserved by the first author available upon request.

Based on these discussions with the German regulatory agency BfArM and to avoid similar disturbances in the future, manufactures of herbal drugs or other herbal medicines are encouraged to submit suspected HILI cases to regulatory agencies only if suspected cases were assessed for causality with the updated RUCAM (9). If regulatory agencies reach different causality gradings, they will have to explain the divergent results.

There was, however, good news from European Medicines Agency (EMA), formerly located in the UK and now in the Netherlands (*Table 4*) that HILI cases attributed to black cohosh were reassessed using RUCAM and denied causality for a variety of reasons in virtually all cases (*Table 4*) (112).

Published HILI cases lacking causality assessment by RUCAM

Regretfully, some otherwise promising and promotional HILI cases did not benefit from causality assessment by RUCAM (*Table 5*) as shown in reports originating from Argentina (114), Austria (115), Belgium (116), Canada (117,118), China (107,119-121), France (121,122), Germany (118,123-131), Italy (132,133). Japan (134), the Netherlands (135), New Zealand (136), South Africa (137), Thailand (138), and the US (139-154). RUCAM could have provided substantial support for published conclusions and provided more power to HILI related issues.

Proposals for improved case management with RUCAM

RUCAM has an excellent run internationally in assessing causality for HILI cases, attributed to its well accepted use worldwide and outperforming over other CAMs. Quality of RUCAM based HILI cases is fairly good but not optimal in some cases. Therefore, in future studies the following points should be considered:

(I) Recommendations as outlined in the updated RUCAM should strictly be followed when assessing

Table 4 RUCAM based HILI reports with negative or rare causality

Country	Author	Year	Initially suspected HILI [n]	Products	Comments
Germany	Teschke (108)	2008	HILI [26]	*Piper methysticum*, syn. Kava	RUCAM was used providing for most cases negative causality gradings: in 18/26 cases, causality for kava was unassessable or excluded; among the remaining 8 cases, a probable causality grading for kava was attributed to 1 patient who adhered on the regulatory daily dose and maximum duration of the therapy, with another patient who received a highly probable causality grading for kava because of a positive result due to an unintentional reexposure, whereas for the remaining 6 cases variable causality gradings for kava ± comedicated drugs were found
	Teschke (109)	2010	HILI [69]	*Actacea racemosa*, formerly *Cimicifuga racemosa*, syn. Black cohosh	Using RUCAM in all 69 cases, in none of the cases a probable or highly probable causality grading was evident; causality for Actacea recemosa was excluded in 27 cases, unlikely in 21, unrelated in 8, and unassessable in 12 cases; only 1/69 cases received a possible causality grading
	Teschke (110)	2012	HILI [15]	*Pelargonium sidoides*	With RUCAM, scores ranged from +5 to –1 points, signifying neither a highly probable nor a probable causality grading for PS in any of the 15 patients: causality for PS was found possible in 3 cases, unlikely in 8, and excluded in 4 cases
	Teschke (111)	2016	HILI [10]	*Petasides hybridus*	Using the updated RUCAM, 9/10 cases received scores from 0 to 2, equivalent to an excluded or unlikely causality grading, whereas for 1/10 cases a score of 3 was attributed, signifying a low graded possible causality grading
United Kingdom	EMA (112)	2007	HILI [47]	*Actacea racemoae*, syn. *Cimicifuga racemose*, syn. Black cohosh	RUCAM used in 31 cases: cases qualified for unassessable, excluded or unrelated causality. RUCAM in additional 16 cases provided causality gradings: excluded in 5 cases (scores between 0 and –2), unlikely (scores between 1 and 2) in 8 cases, possible (scores 3, 4, and 5) in 3 cases, and probable (scores 7 and 6) in 2 cases

EMA, European Medicines Agency; HILI, herb-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method.

HILI cases. These include prospective study design, adherence to LT thresholds, laboratory-based case classification as hepatocellular injury or cholestatic injury, and application of the criteria for assessing cases with an unintentional reexposure. For case presentation, HILI cohorts must be separated from DILI cohorts, the use of the updated RUCAM should be mentioned. Combined application of RUCAM with other CAMs is discouraged. RUCAM based causality gradings must be attributed to each HILI case, and for final evaluation characterization and decision only cases with a probable or highly probable causality gradings should be taken into consideration.

(II) Regulatory causality assessments are problematic in most HILI cases due to lacking use of a robust CAM such as RUCAM. Manufacturers and physicians that intend submitting spontaneous reports of assumed HILI to regulatory agencies are well advised to attach a RUCAM sheet with all relevant case data, scores of each key data element, and the final score with a causality grading. This allows regulatory reassessments and fair discussions with the stakeholders, preventing premature regulatory decision going public, potential loss of regulatory reputation, fruitless discussions in scientific journals, and court hearings.

(III) The HILI community will lose information on HILI characteristics, if HILI case evaluations do not include the use of a robust CAM such as RUCAM. These HILI cases are without scientific value and a waste of time and energy of the authors, aside from financial aspects if studies were supported by governmental funds gathered from taxpayers.

(IV) The recommendations listed above should be

Table 5 Selection of HILI reports lacking causality assessment using RUCAM

Country	Author	Year	Products	Comments
Argentina	Jorge (114)	2005	*Centella asiatica*, syn. Ji Xue Cao	RUCAM was quoted for discussion on reexposure but not used for causality assessment. Thus, causality gradings were not published
Austria	Sperl (115)	1995	*Adenostyles alliariae*	No RUCAM was used nor another CAM, which could have promoted the data of the important HILI case described in an infant following use of this special herbal tea
Belgium	Vanderperren (116)	2005	*Senna angustifolia*	RUCAM was not applied that could have helped assess and establish causality
Canada	Abdualmjid (117)	2013	Multiple herbs	RUCAM of 1993 was not applied for individual causality assessment and defining causality grading, but would have strongly been supportive for the excellent list of herbs assumed to cause HILI
	Bergeron (118)	2019	Traditional herbal medicines	No RUCAM was applied, which could have assisted to establish causality of HILI for the three products that were manufactured in China, India, and Japan but sold in Canada
China	Zhou (107)	2013	Various herbs	No RUCAM was used; RUCAM was neither discussed nor quoted, herbs were listed among complementary and alternative medicines. Lack of RUCAM use invalidates published conclusions
	He (119)	2019	Various herbs	No CAM including no RUCAM was surprisingly used for this otherwise promising report, conditions that invalidate the published conclusions
	Lin (120)	2019	Various herbs	No RUCAM was used although the updated RUCAM was discussed and quoted. With regret and as HILI cases remained without a causality grading, conclusions remain vague of this otherwise promising study
France	Gloro (121)	2005	*Camellia sinensis*, syn. Green tea	No RUCAM was used for this early otherwise excellent case report of HILI by green tea extract, while this important and frequently quoted publication would have strongly benefitted if causality would have been established by using RUCAM
	Kamsu-Foguem (122)	2014	Various herbs	RUCAM was not used but merely quoted and discussed, application of RUCAM could have given more strength to the listed potentially hepatotoxic herbs in Africa
Germany	BfArM, previously online but then removed, now quoted by Teschke 2008 (108), Teschke 2009 (123), Teschke 2010 (124), Teschke 2010 (125), Teschke 2010 (126), Teschke 2011 (127)	2002	*Piper methysticum*, syn. Kava	No RUCAM was used by the Germany regulatory agency BfArM but claims of fragile causality for kava were publicized online by BfArM, which subsequently removed the respective link in the course of scientific fire and due to upcoming legal issues. BfArM's initial removal notice and its statements on the cases can be requested from the first author RT via his email address
	Teschke (128)	2012	Various herbs	No RUCAM was available in listed HILI cases
	Teschke (129)	2013	Various herbs	No RUCAM mentioned in listed HILI cases
	Teschke (130)	2014	Various herbs	No RUCAM available in listed cases of HILI caused by herbal TCMs
	Teschke (131)	2015	Various herbs	No RUCAM mentioned in listed cases of HILI due to traditional and modern herbal medicines

Table 5 *(continued)*

Table 5 *(continued)*

Country	Author	Year	Products	Comments
Italy	Pantano (132)	2016	Kava, Kratom, and Khat	No RUCAM was used for this excellent and stimulating report on partially new HILI by few herbs potentially causing HILI. This report would have benefitted from a strong causality assessment by RUCAM, as also already stated under the limitations section of the study
	Cappelleri (133)	2017	Various herbs	No RUCAM was applied for this interesting report, whereby RUCAM could have assisted identify the herbal culprit
Japan	Adachi (134)	2003	Chaso, Onshido, Green tea extract	No RUCAM was used to establish causality. Discussion arose whether n-nitroso-fenfluramine was the culprit, but green tea extract remained unconsidered, respective reports of HILI by these extracts were not available at time of publication in 2003
The Netherlands	Van Hunsel (135)	2019	Multiple herbs	No RUCAM was applied to 2,483 cases of suspected HILI by herbal medicines, but none of the cases was assessed for causality by any robust CAM. Indeed, the updated RUCAM was discussed and quoted but not used. Problematic is that HILI cases were recruited from the section of hepatobiliary disorders rather than from more specific liver sections
New Zealand	Savage (136)	2019	*Artemisia annua*	No RUCAM was primarily used in any of the cases; instead, alternative evaluation was attempted using the WHO method that is based on global introspection, heavily disputed among experts because this method is by no means not suitable for cases of liver injury. Besides and in 5 cases, the updated RUCAM was used. Overall evaluation is confounded by poor quality of the cases derived from the national database, the mix of two differently qualified CAMs, and the resulting contradictory causality gradings
South Africa	Calitz (137)	2015	Multiple herbs	No RUCAM was used which would have largely improved this otherwise excellent compilation of HILI cases
Thailand	Kanjanahattakij (138)	2019	Multiple herbs	No RUCAM was used, although this report on potentially hepatotoxic plants originating from Thailand could have received more strength by using RUCAM for causality assessment
United States	Mahady (139) from USP	2008	*Actacea racemosa*, formerly *Cimicifuga racemosa*, syn. Black cohosh	No RUCAM was applied by the United States Pharmacopeia (USP); instead, the expert committee used the Naranjo scale, which is not liver specific, lacks validation for liver injury cases and provided a uniform possible causality grading for all 30 cases. This USP report would have benefitted from using the RUCAM of 1993 and avoiding thereby major scientific discussions on methodology issues and highly questionable published conclusions
	Sarma (140) from USP	2009	*Camellia sinensis* syn. Green tea	No RUCAM was used by the United States Pharmacopeia (USP); instead, the Naranjo scale was applied, not validated and not applicable for liver injury cases. Use of RUCAM would have provided robust causality data, which was finally done in a report published 2020
	Engels (141)	2013	Rooibos tea, prepared from *Aspalathus linearis*	No RUCAM was applied, which could have helped provide a valid causality grading in this otherwise interesting case

Table 5 *(continued)*

Table 5 *(continued)*

Country	Author	Year	Products	Comments
	Yarnell (142)	2014	Various herbs	No RUCAM was used for this large listing of potentially herbs, RUCAM use would have enforced valid causality for many of the herbs
	Zheng (143)	2015	Various herbal products	No RUCAM was used or any other CAM allowing individual element scoring, although RUCAM was discussed and quoted. Instead, the DILIN method lacking worldwide use and any individual element scoring was praised as gold standard in the US.
	Hillman (144)	2016	Various herbal products	No RUCAM was applied for causality assessment nor any other CAM allowing individual element scoring, leading to a vague, disputable report
	Lunsford (145)	2016	*Garcinia combogia*	No RUCAM was used for assessing causality but it was required and used only for the R value. Study would have substantially benefitted from RUCAM use and by replacing thereby the global introspection method known as subjective, non-transparent non-element scoring method allowing for vague, percentage causality grading based causality grading only
	Brown (146)	2017	Various herbs	No RUCAM was used for this otherwise excellent, comprehensive online listing of many worldwide used herbs or herbal products that would have substantially benefitted from causality assessment using RUCAM, thereby providing more power on this clinically relevant issue
	Navarro (147)	2017	Various herbal products	No RUCAM was used to validate causality, which could have been provided by RUCAM
	Vega (148)	2017	Various herbal products	No RUCAM was applied that could have facilitated comparison with incidence data obtained from European registries, which included prospective data of RUCAM based cases of liver injury. Instead, the current study used the global introspection method that presents subjective opinions not comparable with the scoring algorithms of the transparent objective RUCAM
	Mousa (149)	2018	*Mitragynia speciosa*, syn. Kratom	No RUCAM was applied, leading to invalid causality assumptions and disputable conclusions, poor scientific conditions for an otherwise important and rare HILI
	Walter (150)	2018	Various herbal products	No RUCAM was used, providing controversial conclusions but RUCAM could have helped establish a valid causality for each of the suspected herbal products and avoid major discussions
	Alyab (151)	2019	Kratom	No RUCAM was used that could have reinforced conclusions presented in this otherwise rare HILI case
	Fernandes (152)	2019	Kratom	No RUCAM was applied for this otherwise important contribution. Use of RUCAM could have helped establish valid causality and foster published conclusions
	Zhu (153)	2019	Various herbal products	An own but not validated CAM was used instead of merely RUCAM that was marginally applied for causality assessment because many other CAMs were simultaneously used, some of these were not specific for liver injury or based on global introspection. This invalidates most of the published conclusions, RUCAM could have helped
	Quinonez (154)	2020	Kratom	No RUCAM was used, providing therefore fragile data and vague conclusions. The use of RUCAM could have assisted enforce robust causality and valid conclusions

BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte, German regulatory agency; CAM, causality assessment method; DILIN, drug-induced liver injury network; HILI, herb-induced liver injury; RUCAM, Roussel Uclaf Causality Assessment Method.

included in national guidelines on diagnosis of HILI. This will ensure comparability of HILI case features among various countries in West and East.

Conclusions

The current analysis presents details of 80 publications on a total number of 12,068 RUCAM based HILI cases from various countries around the world, in line with the user-friendly application of RUCAM smoothly used by reporting physicians and scientists. Among the assessable 11,404/12,068 HILI cases available for further evaluation, causality gradings were highly probable in 4.2% of the cases, probable in 15.5%, possible in 70.3%, and lower graded in 10.0%. To improve the reporting of RUCAM based HILI cases in the future, recommendations include the strict adherence to the instructions outlined in the updated RUCAM and, in particular, to follow a prospective study design to ensure completeness of case data commonly allowing for high causality gradings. In an additional HILI group published in 4 reports, regulatory causality assessments were evidently problematic in virtually all HILI cases due to lacking use of a robust CAM such as RUCAM, but this primarily seems a specific problem of the German regulatory agency, not so of EMA that perfectly evaluated HILI cases using RUCAM. Apart from the 80 reports dealing with RUCAM based HILI cases, there were also 39 publications of HILI cases that did not benefit from causality assessments by a robust CAM like RUCAM. Conclusions derived from these reports have to be used with caution and are not helpful for the HILI community. In conclusion, RUCAM is well accepted in the world to assess causality in suspected HILI cases but additional efforts are now required to increase the quality of the reporting system.

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