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Review Article

Suspected Herb Induced Liver Injury by Green Tea Extracts: Critical Review and Case Analysis applying RUCAM for Causality Assessment

Teschke R[1*] and Xuan TD[2]

[1]Department of Internal Medicine, Division of Gastroenterology and Hepatology, Klinikum Hanau, D-63450 Hanau, Academic Teaching Hospital of the Medical Faculty, Goethe University Frankfurt/ Main, Frankfurt/Main, Germany

[2]Division of Development Technology, Graduate School for International Development and Cooperation (IDEC), Hiro-shima University, Higashi Hiroshima 739-8529, Japan

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***Corresponding to:**

Rolf Teschke, Department of Internal Medicine, Division of Gastroenterology and Hepatology, Klinikum Hanau, D-63450 Hanau, Academic Teaching Hospital of the Medical Faculty, Goethe University Frankfurt/ Main, Frankfurt/ Main, Germany, E-mail: rolf.teschke@gmx.de

1. Abstract

Leaves of green tea (Camellia sinensis) contain EGCG (Epigallocatechin-3-gallate) and other polyphenolic catechins, commonly assumed as harmless and healthy. Whereas the use of the traditional green tea (GT) is in general well tolerated, extracts manufactured from green tea leaves contain large amounts of catechins, mostly as EGCG, being broadly used to reduce or maintain body weight, although a Cochrane study found no significant therapeutical effects. Instead, several reports suggested that the use of green tea extracts (GTE) may carry the risk of herb induced liver injury (HILI), evidenced by serum alanine aminotransferase (ALT) ≥5 x ULN (upper limit of normal) and/or alkaline phosphatase (ALP) ≥2 x ULN. Current critical analyses confirmed that the use of GTE rarely causes HILI, based on causality assessment using RUCAM (Roussel Uclaf Causality Assessment Method) that provided causality gradings of highly probable or probable for published cases. Causality was also verified by unintentional positive reexposure test results. Although the mechanistic steps leading to liver injury have not been explored, evidence exists that GTE may cause idiosyncratic HILI in susceptible users as well as well as intrinsic HILI that is dose dependent. Liver adaptation may also develop, characterized by small increases of liver tests: ALT <5 x ULN and/or ALP <2 x ULN. In conclusion, as the benefit risk assessment is negative, the use of GTE cannot be recommended while no restrictions apply to GT beverages.

2. Keywords: Herb induced liver injury (HILI); Idiosyncratic HILI; Intrinsic HILI; Roussel; Uclaf Causality Assessment Method; RUCAM; Green tea; Green tea extracts; EGCG; Polyphenols; Catechins

3. Abbreviations: ALP; Alkaline Phosphatase; ALT; Alanine Aminotransferase; HILI; Herb Induced Liver Injury; ULN; Upper Limit of Normal

4. Introduction

Green tea manufactured from the leaves of Camellia sinensis (L.) Kuntze is likely one of the most consumed drinks in the world second to water, its use is highly appreciated for its aromatic taste and social functions at gatherings [1]. The abundancy of review articles on green tea concerning clinical reports and biochemical studies is impressive, although robust evidence of clinical efficacy is sparse and controversially discussed [2-5] or not provided [6]. The clinical interest is likely due to the assumption that many diseases as part of human life could have a molecular basis as molecules such as those of the reactive oxygen species (ROS) are largely viewed as contributing culprits [7-10]. The list of potential human diseases assumed as causally related to ROS overproduction is expansive and includes cancer, chronic inflammatory and autoimmune diseases, and more specifically also diabetes mellitus with the metabolic syndrome. If the assumption holds that diseases have commonly a molecular, ROS-based background, then good arguments would be available to prevent and cure diseases using antioxidants, chemically in form of polyphenols that are abundantly found in most plants including vegetables and green tea [5,10-19].

A clear differentiation of green tea (GT) as the commonly consumed beverage is required [1] from high amounts of green tea used as green tea extracts (GTE), introduced as option to reduce weight because obesity related diseases have been associated with ROS as culprits [2,20]. Consecutively, a new era started with additional studies exploring whether GTE could effectively reduce body weight, hopefully without major adverse effects. However, evidence based efficacy was not convincingly presented [20], instead major adverse herb reactions related to the liver and classified as suspected herb induced liver injury (HILI) emerged and became a matter of discussion [2,19,21-23].

The current review article delineates briefly on green tea, their polyphenols as antioxidants and possible role in disease prevention and cure, while the major focus is on liver injury caused by green tea extracts and how to establish causality in reported cases.

5. Literature Search

In order to collect possible cases of liver injury by GT and GTE derived from Camellia sinensis, a selective literature search in PubMed was performed. We used the search terms “green tea”, ”GT”, “Camellia sinensis”, “green tea extract”, and “GTE”, alone and combined with the terms “hepatotoxicity”, “liver injury“, “herbal hepatotoxicity” or “herb induced liver injury”. The search was focused primarily on English language case reports, case series, and clinical reviews, published from 1999 to 11 June 2019. From each search segment, 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.

6. Definitions

6.1 Green Tea Product Categories and Their Catechins

Tea processing describes steps, by which the freshly harvested leaves of the tea plant Camellia sinensis (L.) Kuntze undergo various treatments, resulting in dried leaves ready for storing and brewing [22-24]. Starting from plucking, manufacturing processes of the leaves may include withering, disruption, oxidation, heat fixation, drying and post fermentation, while the extent of the individual manufactural oxidation steps will finally determine one of the different tea product categories with their specific characteristics [22-26]. Tea products include Black Tea, Dark Tea, Green Tea, Oolong Tea, Yellow Tea, and White Tea (**Table 1**) [23]. Product oxidation is accomplished by mechanical disruption of the tea leaves through bruising, rolling, and crushing, followed by disruption of the cellular plant integrity. This then allows free polyphenols to be exposed to oxygen, and the complex oxidation reactions start if the free polyphenols and the peroxidase residing in the plant cellular peroxisomes mix with the polyphenol oxidase in the cytoplasm of the plant cell.

Table 1: Details of various tea products using leaves of *Camellia sinensis*

Products	Manufactural details using leaves of *Camellia sinensis*	References
Black tea	Fresh leaves are allowed to wilt for about 20 hours, during whichmoisture evaporates out of the leaves that imbibe more oxygen from the air. Leaves are then rolled, oxidized via polyphenol oxidase activity and thereby fermented in a humid atmosphere, and dried with hot air.They usually undergo full oxidation syn. fermentation, which results in Their typical black or brown color and in higher caffeine content than less oxidized teas.	[22,23,24]
Dark tea	Dark tea (including Pu'er tea, a special dark tea in China) is a probiotic, unique microbial post-fermented type of tea produced from the sun-derived leaves of the tea species Camellia sinensis (Linn.) var. assamica (Masters).	[24,25,26]
Oolong tea	Oolong tea is a semi fermented tea, wilted, bruised, rolled, followed by partial oxidation (5-40%). It is then pan-fried or steamed to inactivate oxidative enzymes.	[23,24]
Green tea	To obtain green tea, fresh leaves are stabilized by dry heating or steaming to inactivate polyphenol oxidase enzymes and thereby preventing oxidation syn. fermentation, then rolled, rapidly dried, and roasted to some degree. These overall production steps qualifiesgreen tea as an unfermented tea.	[22,23]
Yellowtea	Yellow tea undergoes less oxidation than green tea and benefits from alonger and slower drying period.	[24]
White tea	White tea is manufactured from young leaves or buds, collectedprior to full opening, while the leaflets are picked and allowed to wither lightly before drying that allows a light fermentation.	[22,23]
Green tea extracts	Products are manufactured as water, hydro alcoholic, or ethanolic extracts but the individual manufactural steps are often not described, and ingredients of the extracts are rarely specified.	[2,21,23]

Bioactive phytochemicals of GT and GTE are called catechins [2-5,19] and belong chemically to the large group of polyphenols commonly found with similar chemical polyphenolic structures in most other plants [5,10-15]. As already evident from the name, a polyphenol is a compound that has multiple phenol units, each of these contains six carbon atoms bonded together in a hexagonal ring [5]. Five of the carbon atoms bond with hydrogen atoms, which gives the hydrogen ring a chemical formula C_6H_5. This phenol ring is then bonded to a hydroxyl group – oxygen bonded with hydrogen (OH), resulting in a phenol: C_6H_5OH. The number and characteristics of the phenol units explain the different bioactive properties. Catechins include Epigallocatechin3-gallate (EGCG), Epicatechin (EC), Epicatechin-3-gallate (ECG), and Epigallocatechin (EGC), in descending order of their biological activity [19,22-31], and all are known for their modifying properties of human cytochrome P450 (CYP) and their isoforms (**Table 2**) [27-31]. This explains clinically important interactions between catechins and drugs that are caused at the level of CYP [32,33]. Indeed, patients consuming GT or GTE often use as comedication commercial drugs, other herbal products, or dietary supplements (**Table 3**) [19,34-62]. Comedication of potentially hepatotoxic products is a crucial confounding factor at assessing causality of liver injury connected with the use of GT or GTE [19].

Table 2: Modification of human cytochrome P450 isoforms by green tea, green tea extracts, and their individual catechin constituents.

Green tea/Green tea extracts/Catechins	Clinical/ experimental conditions	Parameter
Green tea	NR	NR
Decaffeinated Green tea	Clinical study: oral intake of capsules for 4 weeks	Human CYP activity CYP1A2 ⟶ [28] CYP2C9 ⟶ [28] CYP2D6 ⟶ 28] CYP3A4 (↓) [28]
	Clinical study:Oral intake of capsules for 2 weeks	Human CYP activity CYP2D6 ⟶ [31] CYP3A4 ⟶[31]
Green extracts	In vitro study: human hepatic microsomes	Human CYP activity CYP2C8 ↓ [27] CYP2B6 ↓ [27] CYP2C9 ↓ [30] CYP2C19 ↓ [27] CYP2D6 ↓ [27,30] CYP3A ↓ [27] CYP3A4 ↓ [30]
	In vitro study human intestinal microsomes	Human CYP activity CYP3A4 ↓ [27]
Epigallocatechin 3-gallate(EGCG)	In vitro study human hepatic microsomes	Human CYP activity CYP2B6 ↓ [27] CYP2C8 ↓ [27] CYP2C19 (↓) [27] CYP2D6 (↓) [27] CYP3A ↓ [27]
	In vitro study human hepatic microsomes	Human CYP activity CYP3A4 ↓ [27]
	In vitro study: membrane fraction of genetically engineered Salmonella typhimurium TA 1538 cells expressing human liver CYP	Human CYP activity CYP1A1 ↓ [29] CYP1A2 ↓ [29] CYP3A4 ↓ [29] CYP2A6 ↓ [29] CYP2C19 ↓ [29] CYP2E1 ↓ [29]
Epicatechin(EC)	In vitro study: membrane fraction of genetically engineered Salmonella typhimurium TA 1538 cells expressing human liver CYP	Human CYP activity CYP1A1 ↓ [29] CYP1A2 ↓ [29] CYP3A4 ↓ [29]
Epicatechin-3-gallate (ECG)	In vitro study: membrane fraction of genetically engineered Salmonella typhimurium TA 1538 cells expressing human liver CYP	Human CYP activity CYP1A1 ↓ [29] CYP1A2 ↓ [29] CYP3A4 ↓ [29]
Epigallocatechin (EGC)	In vitro study membrane fraction of genetically engineered Salmonella typhimurium TA 1538 cells expressing human liver CYP	Human CYP activity CYP1A1 ↓ [29] CYP1A2 ↓ [29] CYP3A4 ↓ [29]

Table 3: Compilation of selected cases reporting suspected liver injury by GT, GTE and comedication.

Authors, Publication Year	Selected Cases (n)	GTE product, composition, brand name	Comedication (prescription or over-the counter)
Gavilan et al., 1999 [34]	1	GT-powdered leaves (Arkocapsulas)	Various herbal teas: Cassia angustifolia, Fucus vesiculosus, Menthapiperita, Equisetum arvense
Seddik et al., 2001 [35]	1	GTE (AR25 EGCG 25%), caffeine 19% (Exolise)	Thicolchicoside, tetrazepam
Thiolet et al., 2002 [36]	1	GT (7%), Oolong tea, C. angustifolia (Oolong tea fine tonic)	Levonorgestrel, ethinylestradiol
Bajaj et al., 2003 [37]	1	GTE and multiple other ingredients (Hydroxycut)	Fluticasone, albuterol
Kanda et al., 2003 [38]	1	Gynostemma Pentaphyllum, Nelumbo Chrysanthemumsp.,Lycium barbarum, Crataegus monogyna, Citrus aurantium, C. mimosoides, Rhaphanus sativus, beer yeast, B1c Golden tang, raifukushi (Be-petite) GT, sp.,	NR
Kanda et al., 2003 [39]	1	GT leaves, Gynostemma pentaphyllum, barbaloin, polyphenol, total saponin (Ohnshidou-genbikounou)	NR
Pedros et al., 2003 [40]	4	All: GTE (EGCG 25%), caffeine 19% (Exolise, Arkopharma)	1. NR 2. Moxifloxacin 3,4NR
Vial et al., 2003 [41]	1	GTE (EGCG 25%), caffeine 19% (Exolise, Arkopharma)	Thyroxine, Benfluorex, Chromocarb, diethylamine
Duenas Sadomil et al., 2004 [42]	1	GTE (EGCG 25%), caffeine 19% (Exolise, Arkopharma)	NR
Garcia-Moran et al., 2004 [43]	1	GT leaves micronized, caffeine >2% (Camilina, Arkocapsulas)	Orthosiphon
Lau et al., 2004 [44]	1	GT leaves, Gynostemma pentaphyllum, Aloe sp. juice, Rhaphanus sativus, Crataegus sp. fruit, N-nitroso-fenfluramine (Slim 10)	NR
Peyrin-Biroulet et al., 2004 [45]	1	GT hydroalcoholic extract containing also Cassia sp. (Mincifit, Arkopharma)	NR
Abu el Wafa et al., 2005 [46]	1	GTE (EGCG 25%), caffeine 19% (Exolise, Arkopharma)	None
Gloro et al., 2005 [47]	1	GTE (EGCG 25%), caffeine 19% (Exolise, Arkopharma)	Bronze Age, paracetamol
Mathieu et al., 2005 [48]	1	GT, C. aurantium, C. paradisi, Cynara scolymus, Petrosileum sativum extracts (x-elles)	None
Porcel et al., 2005 [49]	1	GT leaves, Ananas sativus, maltodextrine, magnesium stearate, silicium dioxide, citric acid (fitofruits grasas acumuladas)	NR
Stevens et al., 2005 [50]	2	Both: GTE with multiple other ingredients (Hydroxycut)	None
Jimenez-Saenz et al., 2006 [51]	1	GT infusion (NR)	None
Javaid and Bonkovsky, 2006 [52]	1	GT infusion (NR)	NR
Bonkovsky, 2006 [53]	1	GTE (Tegreen 97: polyphenols 97%, catechins 64%), Magnolia officinalis, Epimedium koreanum, Lagerstroemia speciosa, calcium, chromium, L-Theanine, b-sistosterol, vanadium (The Right Approach Complex, Pharmanex)	NR
Martinez. Sierra et al., 2006 [54]	1	GT (75%), Mentha piperita (25%) infusion (Tea verde, Hacendado)	NR
Bjornsson and Olsson, 2007 [55]	5	GTE as 82% ethanolic dry extract of Camellia sinensis, Betula alba, Ilex paraguariensis (Cuur Scandinavian Clinical Nutrition)	1. Enalapril 2. Diclofenac 3. Omeprazol 4. Simvastatin, metoprolol, losartan 5. None
García-Cortés et al., 2008 [56]	2	Camellia sinensis (NR)	NR
Shim and Saab, 2009 [57]	1	GTE with multiple other ingredients (Hydroxycut)	Acetaminophen, aspirin, caffeine
Mazzanti et al., 2009 [22]	2	1. GT dry aqueous extract with 90% EGCG (Epinerve Sifi) 2. GT dry aqueous extract with 90% EGCG (NR)	1. Simvastatin, butizide, potassium canrenoate, travoprost 2. Luteinofta
Sharma et al., 2010 [58]	1	GTE with multiple other ingredients (Hydroxycut)	NR
Chen et al., 2010 [59]	1	GTE with multiple other ingredients (Hydroxycut)	None
Rohde et al., 2011 [60]	1	GT, 4 - 6 cups/d (NR)	Levothyroxine, Ca, vitamin D
Navarro et al., 2013 [61]	47	Multiple GTEs with multiple other ingredients	NR
Patel et al., 2013 [62]	1	GTE (Applied Nutrition Green Tea Fat Burner) or EGCG	Whey protein, creatine supplements, GNC Mega Men Sport (Vitamin A, chromium)

6.2. Liver Adaptation and Liver Injury Classification

Abnormal liver tests (LTs) like increased serum ALT (alanine aminotransferase) or ALP (alkaline phosphatase) have been reported in connection with the use of GT or GTE, but the extent of this elevation is often not specifically presented that would allow classify the abnormality as liver adaptation or liver injury (**Table 4**), using a similar approach published previously for the drug induced liver injury (DILI) [63,64] and considering threshold values of liver injury as recommended earlier [64]. Clear distinction of liver adaptation from liver injury is essential as clinical courses and outcomes are different (**Table 4**).

6.2.1. Liver Adaptation: Often misdiagnosed as liver jury or hepatotoxicity due to low clinical awareness, liver adaptation or tolerance in connection with herbal use like GT or GTE represents a mild modification of liver integrity due to metabolic interactions between a chemical and the liver, as evidenced by small increases of liver tests (LTs): aminotransferases and/or ALP (**Table 4**). Most of the commonly used herbs can presumably cause liver adaptation, although this question has rarely been extensively investigated in detail except in small samples of a few cohorts. Similar to herbs, some conventional drugs such as statins and isonicotinic acid hydrazine (INH) can cause liver adaptation, both are

known for triggering also rare idiosyncratic DILI [63], as well as paracetamol, which rarely causes liver adaptation, but mostly induces intrinsic DILI and extremely rare idiosyncratic DILI [65]. Some general features of herb induced liver adaptation are known and listed (**Table 4**).

Table 4: Criteria of liver adaptation and liver injury caused by herbs such as Camellia sinensis.

Mechanistic background	Thresholds of liver tests	Criteria and characteristic features	Recommended description
Adaptive	ALT <5 x ULN ALP <2 x ULN	●Develops at recommended daily doses ●Presumably the majority of herbs have the potency of causing rare but clinically not apparent liver adaptation ●Normalization or stabilization of liver tests is commonly observed whether the herb is discontinued or continued ●With continuation of herb use, there is a rare risk of transition to idiosyncratic HILI	Liver adaptation
Idiosyncratic	ALT ≥5 x ULN ALP ≥2 x ULN	●Caused at recommended daily doses ●Cessation of herb use is obligatory ●Worsening while drug is continued ●Herbs may cause rare idiosyncratic HILI, often called HILI in short if not specified ●Risk of acute liver failure	Idiosyncratic HILI
Intrinsic	ALT ≥5 x ULN ALP ≥2 x ULN	●Emerges soon after acute herb overdose ●Only few herbs are known for causing intrinsic HILI, antidotes are not available ●Risk of acute liver failure	Intrinsic HILI

Modified from a report on drug induced liver injury (DILI) [63]. Note: To meet the respective criterion, thresholds of either ALT or ALP are sufficient. Adapted from a previous report [63], while the threshold values were derived from an earlier publication [64]. Abbreviations: ALP, alkaline phosphatase; ALT, Alanine aminotransferase; HILI, Herb induced liver injury; ULN, Upper limit of normal.

6.2.2. Idiosyncratic and Intrinsic HILI

Liver injury associated with herb treatment such as GT or GTE can be ascribed to the interaction between their phytochemicals and patient factors (idiosyncrasy) or to the herb itself (intrinsic toxicity). In practice, HILI usually represents the idiosyncratic HILI (**Table 4**), which develops among a few individuals under the treatment with a herb used at recommended doses and is caused by unpredictable events due to mostly immunologic and less frequently metabolic herb reactions (**Figure 1**) [64,66,67].

Conditions are different for the intrinsic HILI (**Table 4**), which shows a clear dependency on the herb dose and represents therefore a predictable reaction caused by overdose of the used herb [64,66]. The mechanistic background differs substantially among these two HILI types (**Figure 1**) [66,67]. In a clinical setting, the offending herb(s) often cannot be identified, problems best ascribed to vague principles of diagnosis related to undetermined HILI typology and application of causality assessment methods (CAMs), which do not follow a quantitative and transparent scoring system [66,67] such as the updated RUCAM (Roussel Uclaf Causality Assessment Method) [64].

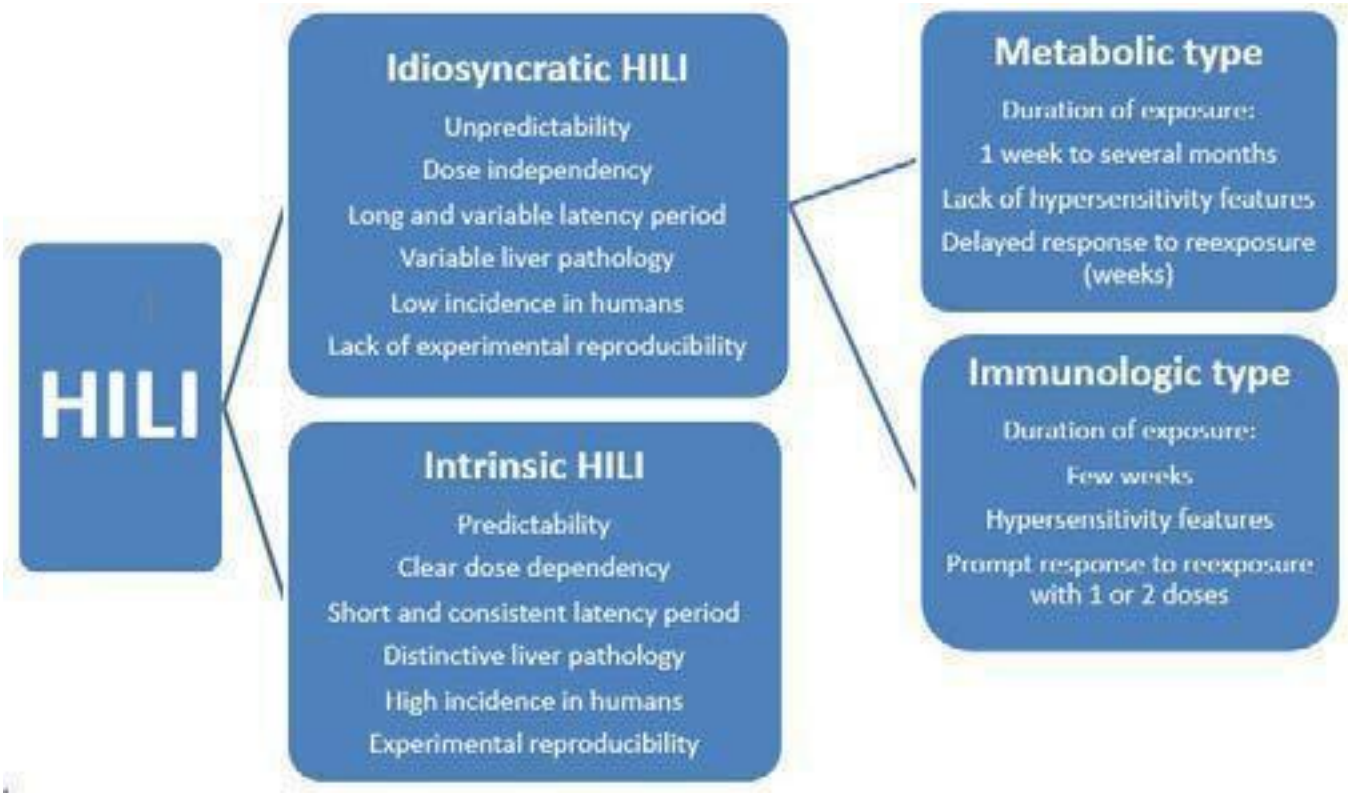

Figure 1: Characteristics of idiosyncratic HILI and intrinsic HILI. Modified from a previous report, originally designed for drug induced liver injury (DILI) [63]. Abbreviation: HILI, Herb induced liver injury.

6.2.3. Thresholds: Assessing the causality in suspected HILI cases, assumed for instance by temporal association with the use of GT or GTE, requires definition of the type of liver injury (Table 4). Currently used criteria of a major liver injury include serum activities of LTs, namely ALT of at least 5 x ULN (upper limit of normal) and/or ALP of hepatic origin and at least 2 x ULN [64]. This specific ALT threshold is important to early recognize and remove all liver adaptation cases with minor and usually reversible liver involvement from the evaluation. Occasionally, lower thresholds of ALT are used, an approach not recommended as this may include unspecific cases; also not correct is using lower thresholds of ALT combined with bilirubin, which is not a parameter of liver injury but of liver function classifying the degree of liver impairment. Diseases to be excluded are for instance those occurring in patients with overweight, obesity or morbid obesity, who have an increased body mass index (BMI) and are at risk of developing nonalcoholic fatty liver disease (NAFLD), or nonalcoholic steatohepatitis (NASH). It is therefore prudent to clear these cases away from the HILI cohorts and focus on real HILI cases, efforts that also will avoid costly diagnostic procedures.

6.2.4. Laboratory defined liver injury

pattern: There is also the need to determine the liver injury pattern. This can be achieved by assessing the ratio R, to be calculated through the multiple of the ULN of serum ALT divided by the multiple of the ULN of serum ALP, provided the ALP increase is clearly of hepatic origin

[64]. The R value allows differentiation of the hepatocellular injury from the cholestatic/mixed liver injury, namely a hepatocellular injury with R >5 from a cholestatic/mixed liver injury with R ≤5. For each injury type a specific RUCAM subscale is available and must be used for causality assessment. This differentiation is essential because risk factors and time courses of ALT and ALP are different, and it also explains why the updated RUCAM scale needs these two subtypes.

7. Causality Assessment of HILI by GT or GTE using RUCAM

A temporal association alone between GT or GTE consumption and emerging liver injury is certainly not sufficient or appropriate to construct any causal association, the preferred approach of regulatory agencies. Instead, a robust CAM is required such as the original RUCAM of 1993 [68] or now better the updated RUCAM of 2016 [64]. RUCAM is the worldwide most commonly used CAM for liver injury with 46,266 cases assessed by the original or updated RUCAM alone between 2014 until early 2019 [63]. RUCAM represents a robust, transparent, liver specific, structured, and quantitative tool providing well defined final causality gradings, which were based on the sum of individually scoring key elements specific for liver injury, whereas other CAMs are either not liver specific or not based on quantitative elements [64]. There is no other CAM, which could outperform RUCAM. This is why RUCAM was used for the cases of HILI by GT or GTE. Many more interesting details of RUCAM have been published [63,64], but additional information or discussion is outside the focus of the current analysis.

8. Published Liver Injury Cases with assumed or questionable Causality for GT or GTE

It is common clinical experience that LT abnormalities found in patients, who used before conventional drugs, herbs, or dietary supplements, are primarily attributed to the use of these products, based on the erroneous assumption that a temporal association equals a causal association. However, causality attribution requires a sophisticated approach, best achieved using RUCAM in its original version [68] and now as the updated RUCAM

[64]. Using the original RUCAM in 12 assessable cases of liver injury by GT or GTE published from 2004 to 2008, causality was highly probable in 5 patients, probable in 6 patients, and possible in one patient, as reported by our group in 2015 [69]. Another and most comprehensive RUCAM based study on liver injury in association with the use of GT or GTE was published by Mazzanti et al. in 2015

[23]. This analysis focused on relevant publications by the end of 2008 to March 2015, involving 19 patients, with a probable causality grading in 8 cases and a possible one in 11 cases. In seven cases, patients used products containing only GT, while twelve patients took multicomponent preparations. The conclusion was reached that a certain safety concern exists with GT, even if the number of liver injury is low. These data extends earlier results by the same group published in 2009 [22] and is in line with previous conclusions of our group

[69]. Of note, few cases with ALT below 5 x ULN were included in the two cohorts, signifying liver adaptation

rather than real liver injury characteristics [22,23]. These conditions require some case reevaluations and modified conclusions.

Of diagnostic value are also increases of LTs following reintroduction of the same product under consideration, an approach known as positive re-exposure test. Support for a causal relationship between liver injury and GT or GTE was also assumed considering cases of positive reexposure syn. re-challenge test results obtained on an unintentional basis but test criteria were not provided that would allow validation of the published data and conclusions [2,21-23]. Indeed, overall robust results of positive re-exposures obtained unintentionally are rarely verified due to reported incomplete data that impede the application of specific diagnostic criteria [70,71]. This shortcoming applies also to liver injury in connection with the use of GT or GTE, shown for 6 patients as examples (**Table 5**).

Table 5: Analysis of reported test results derived from unintentional positive reexposures

Reexposure tests in cases of suspected herb induced liver injury by GT or GTE
● 56-year old French woman [45]: Mincifit® 14 ml/d containing green tea (Camellia sinensis) and Cassia sp. extracts for 15 days. Jaundice. ALT 54 x ULN with R 54.0, normalization of ALT 2 months after cessation. Reexposure 5 years later with Dynasvelte forte® 8 – 12 g/d for 21 days (Green tea, Coffea Arabica, and chromium): ALT 99 x ULN. ALTb<5 x ULN and ALTr≥2ALTb→ positive reexposure.
● 45-year old Spanish man [51]: Green tea infusion (6 cups/day) over 4 months. Asthenia and jaundice of ten days duration prior to cessation. ALT 1613 U/L (normal <40) with R 4.3, ALT normalized within 2 months of cessation. Reexposure 6 weeks later: ALT 1460 U/L after 1 month of reuse. ALTb<5 x ULN and ALTr≥2ALTb → positive reexposure.
● 37-year old Hispanic woman from the US [53]: Green tea-containing product with various other herbal extracts for 4 months. Jaundice. ALT 1788 U/L (normal <40) with R 21.7, ALT 92 U/L after withdrawal. Reexposure one year later for one month: ALT 1131 U/L. ALTb<5 x ULN and ALTr≥2ALTb → positive reexposure.
● 23-year old Spanish woman [56]: Green tea (Camellia sinensis) for 21 days. Jaundice after 19 days. ALT 56.9 x ULN with R 34.7, ALT 0.35 x ULN 3 months after withdrawal. Reexposure: ALT values not available. ALTb<5 x ULN but ALTr not available → uninterpretable reexposure.
● 26-year old Spanish woman [56]: Green tea for 121 days. Jaundice. ALT 32.1 x ULN with R 42.2, ALT dechallenge values not available. Reexposure: ALT values not available. Both ALTb and ALTr not available → uninterpretable reexposure.
● 38-year old French woman [21]: Green tea (six caps Tealine®/d, containing also white and red tea) for 20 days. Symptoms not reported. ALT values not available. Reexposure: Both ALTb and ALTr not available → uninterpretable reexposure.

Compilation of clinical details and laboratory values for assessment of reported positive reexposure test results in selected patients with suspected herb induced liver injury (HILI) by green tea (GT) and green tea extracts (GTE). Data are derived from a previous report, which may provide additional details [67]. Reexposure was commonly unintentional. Criteria for a positive reexposure test result were used as described earlier [64,67], restricted to criteria provided for the hepatocellular type of liver injury [64]. Accordingly, essential data are the ALT levels at baseline before reexposure (ALTb), and the ALT levels during re-exposure (ALTr). Response to re-exposure is positive if ALTr ≥2ALTb and ALTb<5 x ULN, with ULN as the upper limit of the normal value. Other combinations lead to negative or uninterpretable results. Serum enzyme activities were provided in U/L or multiples of ULN. Details for calculation of the R value have been published earlier [64].
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; R, ratio.

Among the 6 patients with published and claimed positive reexposure test, in half of the cases the test data were not usable leading to uninterpretable re-exposure tests, while a positive test result could be confirmed only in the remaining half of the patients (**Table 5**) [69]. It is clear from the present data (**Table 5**) and previous analyses that although a positive re-exposure test is commonly considered as gold standard to diagnoses HILI [64], a cautionary is required if positive tests are published and interpreted [69-71]. Nevertheless, the few cases with verified positive re-exposure tests and with RUCAM based causality gradings of probable and highly probable [69] are suggestive that liver injury by GT or GTE may occur in a few susceptible individuals consuming these products. However, the published case reports did not provide any details on risk factors for these patients experiencing liver injury by GT or GTE.

As an additional important note: Green tea products contain with their catechins different polyphenols in variable amounts that are commonly considered harmless, protective, and healthy due to their antioxidant properties and are by no means expected being toxic to the liver. This raised the question whether high amounts of catechins are needed to injure the liver and to diagnose a liver injury. But there is also concern that the diagnosis of liver injury by GT or GTE may be missed simply due to confounding variables.

9. Evaluation of confounding Variables

It is not unexpected that other cases with assumed liver injury by GT or GTE have previously been listed or discussed [72-76], but several of the published studies may be conflicted with confounding variables that merit and require additional investigative scientific approaches for further conclusions. Some of the confounding variables relate to case evaluation, collecting case data, and the comedication issue, other factors focus on herbal product authentication and quality (Table 6). A stepwise approach was used to search for confounding variables, inconsistencies, and ambiguities that could interfere with the evaluation of suspected HILI by GT or GTE. Confounding variables were found among the cases analyzed in the current study and in cases presented by governmental administrations including regulatory agencies.

Table 6: Inconsistencies, ambiguities and confounding variables interfere with evaluation of suspected HILI by GT or GTE, or they represent risk factors.

Specific key issues	Details	References
Causality assessment method	The United States Pharmacopeia (USP) was the first regulatory agency attempting to assess causality in 34 cases of HILI by GT or GTE, using as CAM not the liver specific RUCAM but the liver unspecific Naranjo. Consequently, USP based case evaluation is highly disputable.	Sarma et al. and USP, 2008 [21]
	No application of the original RUCAM, the updated RUCAM, or any other CAM to verify causality for the presented cases.	LiverTox, 2018 [75]
	Missing use of any CAM including the updated RUCAM in most cases under consideration, although reference is given to a small group of published HILI cases that were assessed by RUCAM.	EFSA Panel, 2019 [2]
	No use of any CAM or the updated RUCAM mentioned for the eleven cases presented, thereby providing vague conclusions.	Health Canada, 2017 [76]
Causality grading	Using the Naranjo method that attributed a possible causality grading to 30 patients and a probable one to 4 cases with an assumed positive reexposure test result.	Sarma et al. and USP, 2008 [21]
	No causality grading provided for any of the presented cases.	LiverTox, 2018 [75]
	For most cases under consideration, no causality grading was presented, except for a few published cases.	EFSA Panel, 2019 [2]
	Lack of any validated causality grading for any of the eleven presented cases.	Health Canada, 2017 [76]
Liver test thresholds	Not specifically defined.	Sarma et al. and USP, 2008 [21]
	Lack of definition.	LiverTox, 2018 [75]
	Missing defined criteria for most cases under consideration.	EFSA Panel, 2019 [2]
	No specific criteria presented.	Health Canada, 2017 [76]
Liver injury type	Lacking definition of the observed liver injury type in any of the cases under discussion.	Sarma et al. and USP, 2008 [21]
	Liver injury type clearly presented for two published cases, sporadically provided for few other reported cases, and assessable for several cases if liver tests are mentioned that would allow evaluation.	LiverTox, 2018 [75]
	Sporadically provided.	EFSA Panel, 2019 [2]
	Not provided.	Health Canada, 2017 [76]
Liver adaptation	Not specifically presented due to lacking search for and not considering any specific criteria.	Sarma et al. and USP, 2008 [21]
	No specific approach recognizable.	LiverTox, 2018 [75]
	Liver adaptation was not specifically addressed.	EFSA Panel, 2019 [2]
	No respective details presented.	Health Canada, 2017 [76]
Reexposure	Positive reexposure tests mentioned for a few cases but without providing specific test criteria. thereby invalidating all respective results.	Sarma et al. and USP, 2008 [21]
	Occasionally mentioned as positive but not evidence based using specific test criteria.	LiverTox, 2018 [75]
	Rarely positive results mentioned but not validated by applying specific criteria.	EFSA Panel, 2019 [2]
	Not described.	Health Canada, 2017 [76]
Comedication	Comedications likely mentioned under the segment of other causes, but no details presented and lack of a transparent scoring system.	Sarma et al. and USP, 2008 [21]
	Comedication not specifically mentioned.	LiverTox, 2018 [75]
	No comedication mentioned and issue not discussed.	EFSA Panel, 2019 [2]
	Not mentioned.	Health Canada, 2017 [76]
Alternative causes	Globally mentioned but not specified.	Sarma et al. and USP, 2008 [21]
	Not presented.	LiverTox, 2018 [75]
	Not provided.	EFSA Panel, 2019 [2]
	Not presented.	Health Canada, 2017 [76]
Authenticity	Mislabeling of GT and GTE products in the US as many products contain no Camellia sinensis or catechins, incorrect information provided in the product label.	Navarro et al., 2013 [61]
Product variability	Plant circadian clock system: Typical for plants, this system may modify plant characteristics and thereby product quality.	Cha et al., 2017 [92]
		Teschke et al., 2018 [90,91]
		Teschke and Xuan, 2019 [5]
	Gut microbiome: Data are available from experimental studies using various chemicals as examples.	Gurley et al., 2019 [102]
		Jung et al., 2019 [103]
	Biotic plant stress: Biotic plant stress is caused by pathogen attacks of other living organisms.	Teschke et al., 2018 [90,91]
		Teschke and Xuan, 2019 [5]
	Abiotic plant stress: As opposed, abiotic stress is of environmental origin unrelated to living organisms.	Elzaawely et al., 2007 [94]
		Xuan et al., 2016 [93]
		Teschke et al., 2018 [90,91]
		Vongdala et al., 2019 [95]
	At the molecular level, both abiotic and biotic plant stress varieties lead to oxidative stress through generation of free radicals including reactive oxygen species (ROS), damaging the plant's integrity and impairing herbal product quality. This occurs if radical scavenging chemicals such as polyphenols are absent in the plant under injurious stress. Plant stress derived ROS influence the quality of herbal products containing higher plants.	Teschke et al., 2018 [90,91]

Abbreviations: CAM, Causality assessment method; GT, Green tea; GTE, Green tea extract; HILI, Herb induced liver injury; ROS, Reactive oxygen species; RUCAM, RousselUclaf Causality Assessment Method; USP, United States Pharmacopeia.

The United States Pharmacopeia (USP) published in 2008 as the first regulatory agency a larger case analysis of suspected HILI by GT or GTE [21], presenting data and conclusions to be reanalyzed due to several confounding variables (**Table 6**). The cohort evaluated by the USP consisted of published cases and regulatory cases from various countries including Canada, Australia, and the US with MedWatch associated with the Food and Drug Administration (FDA) [21], and because the USP presentation has to be viewed as a preliminary approach due to major shortcoming, a further analysis is required for reasons of clarity. First, the quality of HILI cases contained in the MedWatch database is commonly a matter of heavy dispute due to overt shortcomings: variability among the completeness of the reports, some of which consist only of a single sentence with little detail; reports listing the brand without identifying the specific product; absence or lack of FDA access to medical records and past medical histories, partially due to legal restriction; use of other supplements or drug medications at the same time; preexisting or undiagnosed medical conditions; these and other confounding factors were listed, based on specific experience in the US, as detailed in a recent comprehensive review article [72] and another analysis[77] ; in fact, conclusions of both publications are

in line with similar observations regarding the quality of MedWatch cases reported by others [78,79]. Second, USP refuted the use of the liver specific RUCAM to assess causality in the USP study cohort and applied instead the problematic Naranjo method [21] that is not constructed or validated for liver injury cases but commonly used for all kinds of unspecific adverse events, as outlined again recently [64]. US DILI and HILI experts have classified the Naranjo method also as problematic because virtually all cases can reach a possible Naranjo causality grading just because the herbal product has been taken [80]. Third, Naranjo based causality was upgraded to a probable level in four cases by providing 2 extra points for a re-exposure test considered as positive but not substantiated by any appropriate criteria [21]. Fourth, difficult to reconcile was the fact that USP included cases, for which liver injury was not confirmed by objective evidence likely due to missing LTs [21]. Fifth and finally, thresholds for ALT and ALP were not provided to clearly define cases as liver injury rather than as liver adaptation [21]. Expectations are now high that USP members currently use a robust CAM such as the updated RUCAM to reevaluate causality of their suspected HILI cases by GT or GTE [81], a respective USP expert panel meeting was held already from August 31, 2017 – September 2, 2017 in Rockville, MD, USA [82]. Such an updated USP monograph has not yet been published up to now, and its conclusions could therefore not be included in the panel report of the ESPA (European Food Safety Authority), but the panel is aware of the ongoing work on this USP project [2].

The LiverTox database provided a comprehensive list of published case reports and review articles on suspected HILI by GT and GTE, whereby informative case narratives are well appreciated due to illustrating important details in two cases, with marginal details on most other published cases [75]. Lack of using a robust CAM such as the updated RUCAM and defining liver injury criteria limits the online presentation and confound the results of this specific HILI (Table 6), with similar omissions that resulted in problems and recent scientific discussions related also to DILI cases [83–85].

The expert panel of EFSA published in 2018 a comprehensive, critical but balanced opinion report on the safety of green tea catechins with focus on liver injury issues although case analysis was conflicted with confounding variables related to lack of any formal causality assessment in most cases under consideration (**Table 6**) [2]. In addition, some conclusions were based on HILI cases that were vaguely described with increased liver values, which were not quantified and could be ascribed to cases of liver adaptation or liver injury, while other published HILI cases were used with positive re-exposure tests without describing the used test criteria [2]. These omissions invalidate in part the conclusions published by the EFSA panel and ask for an updated scientific opinion.

Health Canada presented eleven cases of suspected liver injury by use of GTE products received from Canada between 2006 and 2016 [76], but data were vague due to confounders (Table 6). These included insufficient data quality and lack of details such as the used CAM and liver injury criteria.

Additional tentative confounders relating to the assumed HILI by GT or GTE should be searched for in the area of comedicated products including other herbal medications, dietary supplements, or conventional drugs with potentially hepatotoxic properties (Table 6) [2,21,75], some of these are presented in a separate list (Table 3) and elsewhere [19]. Although mentioned in many case and regulatory reports, comedications are rarely assessed appropriately for their individual role as causative products in the setting of liver injury by primarily assumed GT or GTE, their role as partial confounders is likely but cannot validly be determined quantitatively in numbers of cases**.** From a clinical and molecular perspective, interactions of catechins with other chemicals can be assumed because they may be initiated by various CYP isoforms (Table 2) that also metabolize most other exogenous chemicals such as drugs [86].

As other typical confounding variables, alternative causes are often detected in case series of DILI [51,87] and HILI [66,69,78,79,88,89]. The issue of alternative causes may also apply to published cases of HILI by GT or GTE (Table 6) [2,22,23,75,76] but this problem has not commonly been identified with the exception of the USP report that globally mentions alternative causes with obscure scorings and without seemingly having major impact on the causality gradings [21].

Many more confounding variables are assumed, recognized or discussed specifically for the GT or GTE products used by individuals who experienced liver injury [2,61]. Confounding variables may also be viewed as potential risk or contributory factors of the liver injury. For GT and GTE products, confounding variables are, for instance: (1) 1,2-unsaturated pyrrolizidine alkaloids (PAs), which may contaminate GT and GTE products caused by co-harvested PA producing plants but the levels of PAs present in green tea products was considered too low to be alone responsible for liver injury [2], certainly a correct statement also in view of the commonly described hepatocellular type of injury in the cases under consideration because PAs typically cause not a simple hepatocellular injury but instead HSOS (hepatic sinusoidal obstruction syndrome);
(2) a large number of GT or GTE products on the US market do not contain green tea or catechins despite announced in the product label [61]; (3) as nature based products GT and GTE lack uniformity due to variability of ingredients and catechin contents, and recommendations are variable how to use these [2,61]; (4) other confounding factors could modify the product quality as known for many herbal products [5,90-92], examples are the circadian clock system in plants that controls many important metabolic pathways including photosynthesis and molecular processes of gene expression in the context of plant circadian rhythms (Table 6) [5,90-92]; or (5) plant stress (Table

6) [5,90,91,93-95], whereby its biotic form is caused by attacks from living organisms while its abiotic variety is the result of conditions originating from the environment like heavy UV radiation, draft, soil contamination by salts or heavy metals taken up by the plants, involving oxidative stress through generation of free radicals including ROS, damaging the plant's integrity.

10. Mechanistic Molecular Considerations, Dose Dependency and Idiosyncrasy

Consensus exists that the mechanistic steps leading to experimental HILI by GT or GTE and possibly transferable to human HILI of patients who consume GT or GTE have incompletely been explored and do not help clarify the essential steps in human liver injury by GT or GTE [2,19,21-23,75,76]. It has correctly been stated that EGCG is the major catechin in GT and GTE products but its role in HILI remains unclear [2]. Having reviewed a wealth of studies on the bioavailability of green tea catechins and metabolic pathways in the intestine and the liver, it was impossible to identify a single mechanistic molecular step responsible for liver injury by green tea ingredients, except that fasting and higher catechin amounts are considered as risk factors [2].

Although the culprit chemical remains vague, the type of the hepatic adverse event is better studied. Based on published cases, GT and GTE are likely causing liver adaptation through a temporal interaction between green tea catechins and the liver, which reacts adaptively upon the presence of the catechins entering the liver cells. These adaptive changes are reversible and clinically not relevant, often remaining unrecognized due to lack of clinical symptoms.

Conditions are different for real liver injury, caused for instance by GT used in normal amounts, allowing the classification of liver injury as one of the idiosyncratic type likely with its metabolic subtype, unpredictable, occurring in susceptible individuals likely due to some genetic modification. In clinical terms, this type of injury is therefore not predictable and cannot be prevented. With GTE, liver injury occurs at higher catechin amounts, not reached if GT is used. Therefore, GTE caused the intrinsic type of liver injury, which is clearly dose dependent, reproducible also in animal studies, and clinically preventable be reducing the amount of ingested catechins.

In the field of experimental liver injuries including those caused by exogenous and potentially hepatotoxic chemicals like alcohol, drugs, and carbon tetrachloride, more experimental but yet less clinical interest has recently focused on the role of the gut microbiome including the gut - liver axis [96-99], and the hepatic circadian rhythms also known as hepatic diurnal variation [97,100,101]. With the gut microbiome and the circadian rhythms, two experimental conditions exist (Table 6). However, it is presently unknown whether these specific conditions are possibly triggering HILI by catechins in humans (Table 6) [102,103].

Several additional aspects merit further discussion, considering more recent publications [104-109]. After oral exposure to green tea, the observed low bioavailability of catechins including EGCG is certainly a crucial issue,

because catechins reach the liver in low amounts [104] but are commonly used in high amounts in studies on hepatotoxicity and cytotoxicity in animal and liver cell models, leading to concern of the validity of the obtained results and their relevance in human HILI by catechins [2,105-108]. Moreover, catechins in experimental studies are used as parent chemicals and not as conjugated compounds that prevail in the liver after conjugation in the intestinal tracts by bacteria or enzymes of intestinal mucosa cells [104]. In this context, it has been emphasized that relative high concentrations of EGCG were found to be toxic for various bacteria. Assuming this is correct, one could argue that toxins derived from intestinal bacteria may trigger the liver injury in a similar way known for endotoxins in alcoholic liver injury in support of intestinal CYP [98]. Intestinal and hepatic CYPs in animals and humans are downregulated by catechins (Table 2) [27-30], but their role in the development of HILI associated with the use of GT or GTE remains speculative.

11. Benefit versus Risk Assessment

11.1. Issue of efficacy

Beverages of green tea with its antioxidant property of polyphenolic catechins are assumed to be associated with various health benefits [2,6] that may include prevention of cancer, obesity, diabetes and neurodegenerative diseases, conclusions addressed in short by the EFSA panel outside the principal scope of safety aspects
[2]. However, respective evidence based clinical or epidemiological results supporting this view are rare or lacking in the relevant peer reviewed scientific literature, contrasting to some positive results obtained by in vitro experimental studies [6]. As an example, clinical relevant anticancer efficacy has not been shown [3,4]. Similarly, the use of GTE that contain high amounts of catechins and caffeine believed to increase energy metabolism has been praised for weight loss and weight maintenance in overweight or obese adults but efficacy remains unclear according the several randomized clinical trials as analyzed in a Cochrane study [20]. There is also lack of evidence that green tea catechins may contribute to longevity in older populations [5]. Overall, efficiency of green tea catechins is marginal at best or not existing.

11.2. Safety concerns

It was not possible to identify an EGCG dose from green tea extracts that could be considered as safe, and uncertainty exists whether prolonged use of GTE may have more serious effects on the liver [2]. Confounding variables as briefly mentioned and listed (Table 6) impair strong conclusions on the risk of liver related adverse events due to the use of GT or GTE [2,19-23,72-76]. Despite these limitations, consensus exists that the traditional green tea beverage consumed in usual amounts is in general well tolerated, occasionally observed small increases of LTs are clinically not relevant and likely of preexisting origin or to be viewed as transient liver adaptation, while real liver injury in a susceptible individual due to idiosyncrasy is theoretically possible but firm evidence is lacking. This contrasts to a few users of GTE, who experience harmless liver adaptation but rarely liver injury, confirmed by positive reexposure tests and RUCAM based causality grading of highly probable or probable.

Fatal outcome has rarely been published but commonly without confirmed causality for GT or GT using RUCAM [2], whereas risks seemed to be marginally increased if GTE was used as part of a product consisting of several compounds, keeping in mind that chances of causality attribution are limited for such multi-compound preparations.

11.3. Benefit risk balance

GT and GTE are without overt benefits for users regarding disease prevention and treatment of any disorder or ailment. Instead and especially regarding GTE, risks like liver injury are much higher than any possible beneficial effect. Clearly, due to genetic predisposition or use in overdose, HILI induced by GT or GTE is a rare occurrence compared to their consumption.

11.4. Recommendations

Green tea consumed in usual daily amounts as traditional beverage requires no specific restriction of its use except perhaps not to consume on empty stomach; experts assume a normal use with 90 – 300 mg EGCG daily whereby the corresponding number of cups depends on the individual EGCG content of the used product
[2]. However, the use of GTE cannot be recommended because risks of liver injury outperform expected benefits.

12. Conclusions

A wealth of studies has focused on both efficacy and adverse events in association with the use of green tea (GT) and green tea extracts (GTE), both are prepared

from the leaves of the plant *Camellia sinensis*. Various beneficial properties such as antioxidant, anticancer, anti-inflammatory, antiimmune, antiobesity, antidiabetes, and antiaging activities have been found in vitro or animal studies, assumed as characteristic positive features of GT, but clinical and epidemiological studies failed to establish efficacy for these claims in humans. Despite these shortcomings, GT is commonly seen as a safe and well tolerated traditional beverage provided it is consumed in normal amounts although extremely rare occurrence of idiosyncratic, dose independent herb induced liver injury (HILI) has been described in very few susceptible individuals. Instead, GTE containing higher amounts of the catechin EGCG and commonly used for weight control may cause rare intrinsic, dose dependent HILI, for which causality was confirmed using the liver specific RUCAM and positive reexposure tests obtained unintentionally by chance and assessed retrospectively using specific test criteria. HILI observed following use of GTE is likely triggered by the EGCG because of its large amounts contained in the extracts although other catechins like EGC or ECG, or even non-catechin compounds cannot be ruled out as causative agents. It is of note that green tea catechins substantially alter the hepatic and intestinal contents and activities of cytochrome P450 (CYP) isoforms at variable degrees. The impact of these CYP modifications on the pathogenenesis and mechanistic steps of the liver injury remains to be established. In essence, based on the hepatotoxicity risk confirmed in the current analysis and the missing efficacy as assessed by a Chochrane analysis, the use of GTE cannot be recommended.

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