

## ORIGINAL ARTICLE

# Thrombocytopenia as an adverse effect of complementary and alternative medicines, herbal remedies, nutritional supplements, foods, and beverages\*

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## Abstract

**Background:** Thrombocytopenia is a well-recognized adverse effect of many drugs. However, the association of thrombocytopenia with complementary/alternative medicines, herbal remedies, nutritional supplements, foods, and beverages has been rarely described, except for reports of thrombocytopenia caused by quinine-containing beverages. **Objectives:** To systematically identify all published reports of thrombocytopenia associated with these substances and to assess the evidence supporting their causal association with thrombocytopenia. **Methods:** Eleven databases were searched to identify relevant published reports. *A priori* criteria were defined for article selection and assessment. Each selected article was independently assessed by the three authors to document the presence of the criteria and determine the level of evidence for a causal association of the reported substance with thrombocytopenia. **Results:** Twenty-seven articles were identified that reported the occurrence of thrombocytopenia with 25 substances (other than quinine). However, only six articles describing five substances (cow's milk, cranberry juice, *Jui* [Chinese herbal tea], *Lupinus termis* bean, and tahini [pulped sesame seeds]) reported clinical data supporting definite evidence of a causal association with thrombocytopenia. Four articles provided probable evidence for four additional substances, and five articles provided possible evidence for five additional substances. In the remaining articles, the association with thrombocytopenia was unlikely or the articles were excluded from review. **Conclusions:** Reports of thrombocytopenia describing definite or probable evidence for an association of a complementary/alternative medicines, herbal remedies, nutritional supplements, foods, and beverages are rare. Whether the occurrence of thrombocytopenia with these substances is uncommon or unrecognized is unknown.

**Key words** thrombocytopenia; drug-induced thrombocytopenia; herbal remedy; complementary/alternative medicine; nutritional supplement; food; beverage

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Use of complementary/alternative medicines, herbal remedies, and nutritional supplements is common but adverse effects are uncommonly documented (1–4). Thrombocytopenia, a well-recognized adverse effect of many drugs approved by regulatory agencies (5, 6), has not been reported in reviews of complementary/alternative medicines (3, 7) and herbal remedies (1, 7). With

the exception of quinine-containing beverages, thrombocytopenia caused by nutritional supplements, foods, and beverages is rarely reported. Patients with thrombocytopenia associated with quinine-containing beverages may have been recognized because quinine is among the most common causes of drug-induced thrombocytopenia (8, 9).

We have previously reviewed all published reports of thrombocytopenia associated with drugs approved by national regulatory agencies using standardized criteria to assess a causal association of the drug with thrombocytopenia (9, 10). These data are continually updated and accessible at the website, <http://www.ouhsc.edu/platelets>. However, articles reporting thrombocytopenia related to complementary/alternative medicines, herbal remedies, nutritional supplements, foods, and beverages have been excluded from our previous analyses. To document what is known, we systematically reviewed all articles reporting thrombocytopenia associated with these substances.

## Methods

### Data sources and searches

Search strategies were designed to identify reports of thrombocytopenia as an adverse effect of complementary and alternative medicines, herbal remedies, nutritional supplements, foods, and beverages. Eleven databases were searched from their inception through June 30, 2009 (Table 1). The ISI Web of Knowledge interface was used to search the [1] Current Contents Connect and [2] Web of Science databases; the OvidSP interface was used to search the [3] Allied and Complementary Medicine (AMED), [4] Cochrane Database of Systematic Reviews, [5] EMBASE, [6] International Pharmaceutical Abstracts, and [7] MEDLINE databases. Reports were also sought from the [8] Natural Medicines Comprehensive Database, [9] FDA MedWatch Database, [10] International Bibliographic Information on Dietary Supplements Database (IBIDS), and [11] the Health and Wellness Resource Center. The websites for these databases are provided in the legend of Table 1. Search strategies included keywords and appropriate subject headings, customized for each resource. Supplemental references were obtained by cross-checking the bibliographies of retrieved articles. The authors' files were searched to identify additional articles. Non-English-language reports were included. Articles were limited to human only.

### Article selection

Articles were selected if they included primary data on patients of any age. Articles were excluded from the review using the four exclusion criteria listed in Table 2. [1] The data reported were insufficient to evaluate the criteria for article assessment. [2] A platelet count  $<100\,000/\mu\text{L}$  was required to provide confidence that the platelet count was significantly less than normal and may be clinically important. [3] The substance described was known to be toxic agent, was illegal, or was avail-

able only for research. An example of a known toxic agent is *Colchicum autumnale*, commonly known as the autumn crocus or meadow saffron (11). Illegal substances, such as cocaine (12) and heroin (13), were excluded because their composition is unknown. An example of nutritional supplement only available for research purposes is Lorenzo's Oil and its component, erucic acid (14, 15). [4] Reports of excessive doses taken with intention for harm were excluded, but otherwise there was no exclusion related to dosage or quantity. For most excluded articles, these exclusion criteria were apparent from the title or abstract and therefore the article was not retrieved for review. Articles in which exclusion criteria were only apparent with review of the text are described in Results.

Because the goal of this review was to be inclusive, the exclusion criteria are less restrictive than for our previous reviews of thrombocytopenia associated with drugs approved by regulatory agencies (9). Differences from our previous criteria are the inclusion of subjects of all ages and of case reports that described subjects with adverse reactions in addition to thrombocytopenia, such as multiple organ toxicities.

### Data abstraction and quality assessment

Criteria for article assessment and definitions of levels of evidence (Table 2) are the same as for our previous reviews (9), with the exception that demonstration of substance-dependent, platelet-reactive antibodies was accepted as a criterion for definite evidence of a causal association with thrombocytopenia in the absence of re-exposure. All three authors independently reviewed each report using a data abstraction form to document the presence or absence of the assessment criteria and to determine the level of evidence for a causal association of the substance with thrombocytopenia. Discrepancies of interpretation were resolved through consensus among the reviewers.

## Results

Twenty-seven articles that described 47 patients with thrombocytopenia associated with 25 substances were selected for our analysis. Because only few reports were identified and because interpretation of the reports was often difficult, a concise summary of each patient report is presented in Tables 3–7. Articles reporting thrombocytopenia associated with quinine-containing beverages were identified but not included in the Tables because quinine is well recognized as one of the most common causes of drug-induced isolated thrombocytopenia (8, 9). In addition to the 27 articles included in the Tables, six articles were identified that described seven patients with

**Table 1** The literature search strategies for each of the 11 databases are summarized indicating the sequence of keywords and/or controlled vocabulary terms (subject headings) used. Subject headings were exploded where indicated by 'exp' and focused when preceded by an asterisk. The following subheadings were included as indicated: *ad*, administration and dosage; *ae*, adverse effects; *ch*, chemistry; *ci*, chemically induced; *co*, complications; *di*, diagnosis; *ep*, epidemiology; *et*, etiology; *po*, poisoning; *to*, toxicity; and *tu*, therapeutic use

Databases	Set	Search string <sup>1</sup>
Current Contents, Web of Science <sup>2</sup>	1	Dietary or Food or Vegetables or Herbs or Vitamins or Traditional
	2	Thrombocytopenia
	3	1 and 2
Allied and Complementary Medicine (AMED)	1	thrombocytopenia.mp
	2	exp Blood Platelets/
	3	1 or 2
Cochrane Database of Systematic Reviews, International Pharmaceutical Abstracts	1	thrombocytopenia.mp
	2	thrombocytopenic purpura.mp
	3	1 or 2
IBIDS <sup>3</sup> , Natural Medicines Comprehensive Database <sup>4</sup> , FDA MedWatch <sup>5</sup>	1	thrombocytopenia
	2	thrombocytopenic purpura
	3	1 or 2
EMBASE	1	Food Additive/or exp Food/or Health Food/
	2	exp Vitamin/or Diet Supplementation/or Herbaceous Agent/
	3	1 or 2
	4	exp Thrombocytopenia/di
	5	3 and 4
Health and Wellness Resource Center <sup>6</sup>	1	Symptom search: thrombocytopenia
	2	Symptom search: thrombocytopenic purpura
MEDLINE	1	exp Thrombocytopenia/di, co, ci, pa, ep, et
	2	*Nonprescription Drugs/ad, tu, to, ae, po, ch
	3	Plants/or Plants, Medicinal/or exp Plants, Edible/or Plants, Toxic/
	4	exp Plant Extracts/or exp Phytotherapy/or *Plant preparations/ae
	5	Vegetables/or exp Fruit/or exp Food/or exp Beverages/or *Food, Fortified/or *food hypersensitivity/
	6	exp Diet/or exp Dietary Supplements/or exp Vitamins/or Drugs, Chinese Herbal/
	7	*Quinine/ae
	8	Medicine, Chinese Traditional/or Medicine, Traditional/or Medicine, Unani/or Medicine, African Traditional/or Medicine, East Asian Traditional/or Herbal Medicine/or Medicine, Arabic/or Medicine, Korean Traditional/or Medicine, Ayurvedic/or Medicine, Tibetan Traditional/
	9	or/2–8
	10	1 and 9

<sup>1</sup>'Search string' indicates the sequence of keywords and/or subject heading terms used. The websites for the databases are the following:

<sup>2</sup><http://isiwebofknowledge.com/> then choose ISI Web of Knowledge, Current Contents and Web of Science. Accessed through the University of Oklahoma Health Sciences Center Robert M. Bird Library's subscription on June 30, 2009.

<sup>3</sup><http://grande.nal.usda.gov/ibids/index.php>. Accessed on June 30, 2009.

<sup>4</sup>[http://www.naturaldatabase.com/\(S\(bwaywaeqmem3jezsbcasyn55\)\)/nd/products.aspx?s=ND](http://www.naturaldatabase.com/(S(bwaywaeqmem3jezsbcasyn55))/nd/products.aspx?s=ND). Accessed through the University of Oklahoma Health Sciences Center Robert M. Bird Library's subscription on June 30, 2009.

<sup>5</sup><http://www.fda.gov/Safety/MedWatch/default.htm> Accessed on June 30, 2009.

<sup>6</sup>[http://galenet.galegroup.com/servlet/HWRC/form;jsessionid=CE0AC7CE4BB0624B901FB37E8931AB0F?bucket=drugherb&n=10&l=6&seg=0&lo-clD=uoo\\_bird&finalAuth=true](http://galenet.galegroup.com/servlet/HWRC/form;jsessionid=CE0AC7CE4BB0624B901FB37E8931AB0F?bucket=drugherb&n=10&l=6&seg=0&lo-clD=uoo_bird&finalAuth=true). Accessed through the University of Oklahoma Health Sciences Center Robert M. Bird Library's subscription on June 30, 2009.

**Table 2** Criteria for article assessment, the interpretation of the criteria to determine the level of evidence for a causal association with thrombocytopenia, and criteria for excluding case reports from assessment. Levels of evidence were assigned in a hierarchical sequence

	Description
Criteria for article assessment	
1	1) Ingestion of candidate substance preceded thrombocytopenia, <i>and</i> 2) Platelet count recovered to normal or to the baseline level if the patient had an established disorder with chronic mild thrombocytopenia
2	1) Candidate substance was only suspected agent ingested prior to onset of thrombocytopenia <i>or</i> 2) Other agents were ingested prior to onset of thrombocytopenia but were reintroduced, or continued, after discontinuation of candidate substance with sustained normal platelet count
3	Other etiologies for thrombocytopenia were excluded
4	Re-exposure to the substance resulted in recurrent acute thrombocytopenia
5	Substance-dependent platelet-reactive antibodies were identified
Levels of evidence	
1 [Definite]	Criteria 1, 2, 3, 4 <i>or</i> 1, 2, 3, 5 met
2 [Probable]	Criteria 1, 2, 3 met, <i>but not</i> criteria 4 <i>or</i> 5
3 [Possible]	Criterion 1 met, <i>but not</i> criteria 2 <i>and</i> 3, <i>and not</i> criteria 4 <i>or</i> 5
4 [Unlikely]	Criterion 1 not met <i>or</i> re-exposure does not result in recurrent thrombocytopenia
5 [Excluded]	Criteria for excluding articles from review: 1. Insufficient data to evaluate an association between the reported substance and thrombocytopenia 2. Platelet count not $<100\ 000/\mu\text{L}$ 3. Substance is known to be [a] toxic, [b] illegal, or [c] is available only for research 4. Substance was taken as an overdose with intention to harm

**Table 3** Substances with definite evidence for a causal association with thrombocytopenia. Each case report begins with the subject's age (yr) and gender (M/F). The case summaries document the basis for determining the level of evidence, according to the criteria presented in Table 2. Articles are listed in alphabetical order of the reported substance

Substance	Case report summary
Milk (22)	33 M with ulcerative colitis developed thrombocytopenia ( $5 \times 10^3/\mu\text{L}$ ) and rectal bleeding requiring transfusions. Platelet count recovered after food intake discontinued and remained normal until cow's milk was added to diet; then thrombocytopenia recurred ( $150$ to $11 \times 10^3/\mu\text{L}$ ). Platelet counts remained normal and ulcerative colitis resolved with a milk-free diet
Cranberry juice (23)	68 M developed thrombocytopenia ( $1 \times 10^3/\mu\text{L}$ ) with mucocutaneous bleeding and hematuria. Platelet counts recovered to normal ( $200 \times 10^3/\mu\text{L}$ ) with steroid treatment. Dietary history suggested cranberry juice, taken for 10 d for urinary retention, was associated with the thrombocytopenia. Using indirect immunofluorescence, cranberry juice-dependent platelet-reactive IgG and IgM antibodies were detected using dialyzed juice of the same brand and batch. Challenge with cranberry juice not reported
Jui herbal tea (24)	51 F developed thrombocytopenia ( $16 \times 10^3/\mu\text{L}$ ) with mucocutaneous bleeding associated with <i>Jui</i> herbal tea taken several days before her annual health examination. Challenge with <i>Jui</i> caused thrombocytopenia ( $305$ to $2 \times 10^3/\mu\text{L}$ ) within 1 d
Jui herbal tea (25)	54 M with liver cirrhosis had 3 episodes of thrombocytopenia with platelet counts of zero and mucocutaneous bleeding. Association with <i>Jui</i> was noted. Platelet counts following recovery from each episode are not reported but are described as 'his usual range'. Challenge with <i>Jui</i> caused the platelet count to rapidly decrease to zero in 6 h and recovered to 'prechallenge levels' on day 6. Thrombocytopenia did not recur after stopping <i>Jui</i>
<i>Lupinus termis</i> bean (26)	13 M developed thrombocytopenia on 5 occasions after <i>L. termis</i> bean ingestion, 3 times as a supervised challenge with a single bean. At the last challenge, the platelet count decreased from 160 to $10 \times 10^3/\mu\text{L}$ in 2 h. Recovery platelet counts not reported
Tahini (27)	28 F with multiple episodes of thrombocytopenia (lowest platelet count, $6 \times 10^3/\mu\text{L}$ ) with mucocutaneous bleeding. The patient associated thrombocytopenia with ingestion of tahini. Following challenge, the platelet count fell from 161 to $34 \times 10^3/\mu\text{L}$ in 1 d and recovered ( $189 \times 10^3/\mu\text{L}$ ) in 9 d

thrombocytopenia associated with quinine-containing beverages (16–21). Tonic water was the source of quinine in six patients (16–19, 21); quinine in Dubonnet appetif caused recurrent thrombocytopenia in one of these patients (19); and Sparkling Bitter Lemon was the source of quinine in the other patient (20). In six of the seven

patients, the evidence for a causal association of quinine with thrombocytopenia was definite because recurrent episodes of thrombocytopenia occurred in four patients (16, 18–20) and quinine-dependent, platelet-reactive antibodies were documented in five patients (16–18, 20). In the other patient the evidence level was probable (21).

**Table 4** Substances with probable evidence for a causal association with thrombocytopenia. Each case report begins with the subject's age (yr) and gender (M/F). The case summaries document the basis for determining the level of evidence, according to the criteria presented in Table 2. Articles are listed in alphabetical order of the reported substance

Substance	Case report summary
Bajiaolian (28)	38 F (Case 2) developed thrombocytopenia ( $70 \times 10^3/\mu\text{L}$ ) and leukopenia ( $2270/\mu\text{L}$ ) in addition to ataxia and paresthesias 2 h after drinking Bajiaolian infusion. Platelet count recovered to normal ( $227 \times 10^3/\mu\text{L}$ ) in 12 d, leukopenia in 25 d, but paresthesias persisted. Criteria 1, 2, and 3 were met
<i>Cupressus funebris</i> (Mourning cypress) (29)	62 F developed acute systemic illness [acute renal failure, liver toxicity, hemolytic anemia and thrombocytopenia (nadir, $2 \times 10^3/\mu\text{L}$ on day 4)] 2 h after ingesting hot water extract from sliced wood ( <i>C. funebris</i> ). Her first ingestion 1 wk previously had caused no symptoms. 'Recovery from thrombocytopenia within days' is stated but no recovery platelet counts are reported. Increased serum creatinine persisted for >1 month. Criteria 1, 2, and 3 were met
Milk, Potato (30)	26 F (Case 2) with repeated episodes of nausea, vomiting, and bloody diarrhea associated with thrombocytopenia; milk, and potato were suspected etiologies. Challenge with potato: platelet count decreased from 104 to $91 \times 10^3/\mu\text{L}$ at 30 min. Challenge with milk: platelet count decreased from 56 to $46 \times 10^3/\mu\text{L}$ at 30 min. Following elimination of milk and potatoes from her diet, platelet counts were 140 to $190 \times 10^3/\mu\text{L}$ for the following 9 months. Criteria 1, 2, and 3 were met; challenge criterion not met
Vitamin A palmitate (31)	3- month-old M developed thrombocytopenia ( $30 \times 10^3/\mu\text{L}$ ) and anemia. Marrow aspirate demonstrated decreased megakaryocytes and erythroid dysplasia. He had received 62 000 U of vitamin A each day (41-times the recommended requirement) since 10 d of age because of misunderstood instructions. Platelet count recovered to $220 \times 10^3/\mu\text{L}$ 30 d after vitamin A stopped. Criteria 1, 2, and 3 were met

**Table 5** Substances with possible evidence for a causal association with thrombocytopenia. Each case report begins with the subject's age (yr) and gender (M/F). The case summaries document the basis for determining the level of evidence, according to the criteria presented in Table 2. Articles are listed in alphabetical order of the reported substance

Substance	Case report summary
Chromium picolinate (33)	33 F developed acute renal failure, liver toxicity, hemolytic anemia, and thrombocytopenia ( $15 \times 10^3/\mu\text{L}$ ) after taking chromium picolinate tablets for 4–5 months for weight loss. Plasma chromium concentration was more than twice normal. Platelet count and other abnormalities returned to normal by day 26 after stopping chromium tablets. Criteria 1 met; insufficient data to assess criteria 2 and 3
<i>Echinacea pallida</i> (34)	32 M used <i>E. pallida</i> for treatment of a respiratory infection for 1 wk. Paracetamol was also used. Two weeks after stopping <i>Echinacea</i> he developed thrombocytopenia ( $20 \times 10^3/\mu\text{L}$ ), microangiopathic hemolytic anemia, and seizures. He recovered following 1 month of plasma exchange treatment. Criterion 1 met; insufficient data to assess criteria 2 and 3
<i>Hypericum perforatum</i> (St. John's Wort) (35)	22 M was admitted to hospital with fever, pharyngitis, anemia (6 g/dl), agranulocytosis (absolute neutrophil count, $12/\mu\text{L}$ ). He had been taking St. John's Wort for 3 wk and fluoxetine for 3 months for depression. Thrombocytopenia developed on day 3 ( $464$ to $83 \times 10^3/\mu\text{L}$ ). Marrow biopsy demonstrated necrosis. The patient died on day 8. Although platelet count did not recover, criterion 1 may have been met if the patient had survived. Criteria 2 and 3 not met; a viral infection etiology as well as St. John's Wort toxicity was considered
Nicotinamide (36)	Patient (age, gender not reported) developed thrombocytopenia (platelet count decreased from 168 to $83 \times 10^3/\mu\text{L}$ ) after 12 wk of treatment with nicotinamide for hyperphosphatemia while on chronic hemodialysis. Platelet count recovered to $180 \times 10^3/\mu\text{L}$ 2 wk after nicotinamide discontinued. Criteria 1 met; insufficient data to assess criteria 2 and 3
Complete Thymic Formula (37)	Patient (age, gender not reported) with hepatitis C developed thrombocytopenia ( $4 \times 10^3/\mu\text{L}$ ) following 5 months use of the dietary supplement, Complete Thymic Formula. The patient was also taking naproxen; both were discontinued and 'the platelet count returned to baseline'. Criteria 1 met; insufficient data to assess criteria 2 and 3

Six articles reported single patients with data providing definite evidence for a causal association with thrombocytopenia for five substances (Table 3) (22–27). Each of these patients had severe, isolated thrombocytopenia, with nadir platelet counts of  $0$ – $16 \times 10^3/\mu\text{L}$ . In five articles describing four substances [cow's milk (22), *Jui* (a Chinese herbal tea) (24, 25), *Lupinus termis* (a bean grown in North Africa and Mediterranean regions, known as 'white lupin' or 'turmus') (26), and

tahini (pulped sesame seeds) (27)], a controlled challenge with the suspected substance documented that the substance caused thrombocytopenia. One substance, cranberry juice, fulfilled the criteria for definite evidence for a causal association with thrombocytopenia by documentation of platelet-reactive antibodies that were dependent on the presence of dialysate of cranberry juice that was obtained from the same brand and batch that had been consumed by the patient (23).

**Table 6** Substances with an unlikely association with thrombocytopenia. Each case report begins with the subject's age (yr) and gender (M/F). The case summaries document the basis for determining the level of evidence, according to the criteria presented in Table 2. Articles are listed in alphabetical order of the reported substance

Substance	Case report summary
Bajiaolian (28)	3 patients (Cases 3–5) developed thrombocytopenia ( $20\text{--}56 \times 10^3/\mu\text{L}$ ) after drinking Bajiaolian infusions, but data on recovery from thrombocytopenia are not reported, therefore criterion 1 not met. All 3 patients also had neurologic abnormalities
Kelp (38)	54 F developed thrombocytopenia ( $16 \times 10^3/\mu\text{L}$ ) with mucocutaneous bleeding after 6 wk of kelp tablets (that contained $1.3 \mu\text{g/g}$ arsenic) and a multivitamin. Marrow aspirate demonstrated normal megakaryocytes and dyserythropoiesis. Platelet count recovered to $60 \times 10^3/\mu\text{L}$ with treatment with steroids and azathioprine. Complete recovery not reported; criterion 1 not met
Milk (39)	F, age 10–60 d, born with thrombocytopenia-absent radius syndrome had recurrent diarrhea, eosinophilia, and thrombocytopenia associated with 2 periods of cow's milk feeding. Diarrhea and eosinophilia, but not thrombocytopenia, recurred with a third introduction of cow's milk. Criteria 1 and 4 not met
Milk (40)	Infant M born to mother with ITP had platelet count of $11 \times 10^3/\mu\text{L}$ at birth that persisted, in spite of steroid treatment for 11 wk, when milk stopped because of diarrhea. Platelet count increased from 11 to $150 \times 10^3/\mu\text{L}$ after 6 d (3 d, no milk; 3 d half-strength milk). After 10 d on normal milk, platelet count $30 \times 10^3/\mu\text{L}$ ; 3 wk after stopping milk, platelet count $200 \times 10^3/\mu\text{L}$ . Milk resumed at age 1 yr when platelet count $300 \times 10^3/\mu\text{L}$ ; mother reported bruising after 2 attempts to resume milk; no platelet counts reported. The challenges with milk appeared to fulfill criterion 4 but the diagnosis was uncertain because of the mother's ITP and the unspecified nature of the milk products
Niacin (nicotinic acid, vitamin B3) (41)	51 M (Case 2) developed thrombocytopenia ( $92 \times 10^3/\mu\text{L}$ ) and leukopenia ( $2.1 \times 10^3/\mu\text{L}$ ) while taking 2.5 g/d nicotinic acid for about 3 yr. Platelet counts increased after stopping nicotinic acid, but remained low ( $118 \times 10^3/\mu\text{L}$ ) 2 months later. Criterion 1 not met
Herbal 'Ultimate Colon Cleanse Program™' (42)	51 F developed thrombocytopenia ( $24 \times 10^3/\mu\text{L}$ ), neutropenia ( $24 \times 10^3/\mu\text{L}$ ), and anemia (8.5 g/l) following 30 d of this product which contained 39 different herbal ingredients. Marrow aspirate demonstrated aplasia (<5% cellularity). No follow-up reported. Criterion 1 not met

Four articles reported four patients with data providing probable evidence for a causal association with thrombocytopenia for five substances (Table 4) (28–31). Only one of these patients, whose thrombocytopenia was apparently associated with ingestion of milk and potatoes (30), had isolated thrombocytopenia. Although milk and potato were identified by controlled rechallenges with these foods, the rechallenges did not fulfill our *a priori* criteria because the platelet counts prior to the rechallenges were not normal and the changes of the platelet counts were minimal; also, the accuracy of platelet counts in 1935 is uncertain (30). The other three patients did not meet the criteria for a definite association because there was no rechallenge with the suspected substance or documentation of substance-dependent, platelet-reactive antibodies. These other three patients all had systemic toxicities in addition to thrombocytopenia. The patient who developed thrombocytopenia following Bajiaolian, a Chinese herbal tea made from the root of *Dysosma pleianthum*, a species of Mayberry, also had leukopenia and persistent neurologic abnormalities (28). The patient who ingested an extract of Mourning Cypress wood (29) had a systemic disorder similar to the syndrome of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) associated with quinine (32), with acute renal failure, liver toxicity, and hemolytic anemia in addition to thrombocytopenia. The

infant who was treated with excessive vitamin A developed marrow aplasia (31).

Five articles reported five patients with data providing possible evidence for a causal association with thrombocytopenia for five substances (Table 5) (33–37). Two patients had isolated thrombocytopenia, associated with nicotinamide (36) and with a dietary supplement termed 'Complete Thymic Formula' (37). The patients who ingested chromium picolinate (33) and *Echinacea* (34) developed severe systemic disorders resembling TTP-HUS, similar to quinine toxicity (32) and to the patient described earlier with Mourning Cypress toxicity (29).

Six articles described eight patients for whom the reported data suggested that a causal association of five substances with thrombocytopenia was unlikely (Table 6) (28, 38–42). In one patient, a third rechallenge with cow's milk did not cause recurrent thrombocytopenia even though thrombocytopenia had apparently recurred with two previous exposures to cow's milk (39). In the other seven patients, platelet count recovery was incomplete or follow-up platelet counts were not reported (28, 38, 40–42).

The remaining eight articles that described thrombocytopenia in 24 patients in association with 11 substances were excluded from review only after review of the complete text (Table 7) (30, 43–49). The report of four patients with thrombocytopenia apparently associated with aspartame described recurrent thrombocytopenia in

**Table 7** Substances in reports that were excluded from analysis. Each case report begins with the subject's age (yr) and gender (M/F). The case summaries document the basis for determining the level of evidence, according to the criteria presented in Table 2. Articles are listed in alphabetical order of the reported substance

Substance	Case report summary
Aspartame (43)	Case 1: 10 F developed thrombocytopenia ( $1 \times 10^3/\mu\text{L}$ ) and hepatosplenomegaly that resolved when aspartame stopped. Two recurrences after ingesting aspartame 'with remissions when abstaining from aspartame', but no data reported. Case 2: 11 F developed thrombocytopenia after chewing aspartame gum; resolved when aspartame was stopped; recurred with aspartame candy. No data reported. Case 3: 61 M developed thrombocytopenia ( $54 \times 10^3/\mu\text{L}$ ) after drinking diet colas for 2 yr; resolved when aspartame stopped; 'retest trial resulted in an immediate exacerbation'. No data reported. Case 4: F (age not reported) developed thrombocytopenia ( $30 \times 10^3/\mu\text{L}$ ) with hypertension following pregnancy while drinking diet colas; resolved when aspartame stopped. There is insufficient data in these small patient descriptions to assess criteria
Chinese herbal medicine (44)	Patient (age, gender not reported) developed thrombocytopenia ( $3 \times 10^3$ platelets/ $\mu\text{L}$ ) with mucocutaneous bleeding. 'The patient had taken an unidentified Chinese herbal medicine.' No additional data reported
Foods (cocoa, egg, potato, wheat) (30)	5 case reports excluded because of insufficient evidence to assess criteria (Case 3) or platelet counts not $<100 \times 10^3/\mu\text{L}$ (Cases 1, 4, 5, 6)
<i>Garbhajal ras</i> (45)	F (age no reported) presented with thrombocytopenia after repeated use of this Ayurvedic medicine that contained multiple metals and herbal preparations. No platelet count data reported
Niacin (nicotinic acid, vitamin B3) (46)	32 M developed thrombocytopenia ( $118 \times 10^3/\mu\text{L}$ ) and liver toxicity after taking niacin and other vitamins for 10 yr. Niacin stopped; other vitamins continued; platelet count recovered to $193 \times 10^3/\mu\text{L}$ in 11 d; serum transaminase levels also returned to normal. Excluded because platelet count not $<100 \times 10^3/\mu\text{L}$
Nicotinamide (47)	6 patients on hemodialysis with hyperphosphatemia treated with nicotinamide, 1000 mg/d; 5 developed thrombocytopenia (mean values: $188 \pm 17 \times 10^3/\mu\text{L}$ before therapy; $122 \pm 41 \times 10^3/\mu\text{L}$ within 3 months of beginning nicotinamide; $150 \pm 9 \times 10^3/\mu\text{L}$ 10 d after discontinuing nicotinamide. Excluded because data are insufficient to meet criterion for platelet count $<100 \pm 9 \times 10^3/\mu\text{L}$
Sho-saiko-to (48)	67 M with hepatitis C developed thrombocytopenia ( $5 \times 10^3/\mu\text{L}$ ) with mucocutaneous bleeding. Thrombocytopenia improved with intravenous immunoglobulin and steroid treatment, but platelet counts are not reported. Exposure 1 yr previously was also associated with thrombocytopenia ( $98 \times 10^3/\mu\text{L}$ ). Reported data are insufficient to assess Criterion 1
Traditional African herbal remedies (49)	5 patients reported who had 'complete absence of platelets' on the peripheral blood film. Excluded because of insufficient evidence to assess criteria

three patients, but the brief patient summaries did not provide information about platelet counts or the time of thrombocytopenia in relation to aspartame ingestion (43). In the report of thrombocytopenia associated with Sho-saiko-to ('Formula bupleuri minor'), a Chinese remedy made from seven different herbal preparations), the thrombocytopenia was not distinguished from autoimmune thrombocytopenic purpura, and the history of previous exposure associated with mild thrombocytopenia (platelet count,  $98\,000/\mu\text{L}$ ) was not distinguished from the baseline platelet count in this patient with chronic hepatitis C (48). In the remaining 20 case reports there was either insufficient data to document the assessment criteria (nine case reports) or the platelet count was never  $<100\,000/\mu\text{L}$  (11 case reports, including one article describing six patients only as group data with a mean nadir platelet count of  $122\,000/\mu\text{L}$  (47)).

## Discussion

Drug-induced thrombocytopenia is commonly reported (5, 6, 9). In our continuing systematic reviews of published reports of drug-induced thrombocytopenia through 2008, we have identified 317 drugs in 1207 individual patient

reports and an additional 116 articles reporting group data; 88 (28%) of these 317 drugs had a causal association with thrombocytopenia supported by reports with evidence for a definite association or two or more reports with evidence for a probable association. These data, together with data describing each individual patient report, are accessible at <http://www.ouhsc.edu/platelets> (9, 10).

In comparison with drug-induced thrombocytopenia, reports of thrombocytopenia associated with complementary/alternative medicines, herbal remedies, nutritional supplements, foods, and beverages are surprisingly few, with the exception of reports of thrombocytopenia associated with quinine-containing beverages (16–21). The 27 articles identified in our study reported on 25 substances other than quinine from 12 different countries; their publication spanned 72 yr. The number of reports identified was small in spite of our use of less stringent criteria for article and patient selection than we have used in our previous reviews of drug-induced thrombocytopenia, which include only reports of isolated thrombocytopenia (9). Among the 23 patients in Table 3 who were not excluded from analysis, only 12 had isolated thrombocytopenia. The other 11 patients had thrombocytopenia as one component of a systemic disorder; three of these 11

patients had a disorder resembling TTP-HUS (29, 33, 34), similar to quinine-induced TTP-HUS that manifests acute renal failure, liver toxicity, and microangiopathic hemolytic anemia in addition to thrombocytopenia (32).

A strength of this study was the comprehensive search strategy to attempt to identify all published reports that may have described patients with thrombocytopenia associated with complementary/alternative medicines, herbal remedies, nutritional supplements, foods, and beverages. A limitation of this study was the difficulty assessing the case reports. Even with *a priori* development of explicit criteria for objectively assessing each patient report, and even with independent assessments of each article by three reviewers, there was often uncertainty about level of evidence. Many articles did not explicitly describe data required to assess our criteria, and judgment was required to interpret the reported data. However, the conclusion of our study was clear: there are very few published reports of thrombocytopenia associated with these substances.

There are several possible reasons for the few reports of thrombocytopenia with complementary/alternative medicines, herbal remedies, nutritional supplements, foods, and beverages. (i) The absence of well-documented reports clearly describing an association of thrombocytopenia with these substances may lead to lack of suspicion of a possible association. The recognition of quinine-containing beverages as a cause of isolated thrombocytopenia (16–21) is an exception and may only occur because of familiarity with quinine as one of the most common causes of drug-induced thrombocytopenia (8, 9). (ii) When clinicians ask their patients about the medicines they are taking, they often do not explicitly ask about complementary/alternative medicines, herbal remedies, and nutritional supplements. When clinicians do ask about these substances, patients may be reluctant to report their use. (iii) Complementary/alternative medicines, herbal remedies, and nutritional supplements are often considered to be 'natural' and therefore safe, diminishing the suspicion for adverse effects (1). (iv) Persons who prescribe complementary/alternative medicines and herbal remedies may not be familiar with the process of publication of case reports. (v) There has been no standard for reporting patients with thrombocytopenia that may have been associated with these substances. This has resulted in many patient reports with insufficient data to document a causal association. (vi) Some substances described in these articles, such as the *L. termis* bean (26), may only be used in limited regions of the world.

Finally, thrombocytopenia may actually be a rare adverse effect of complementary/alternative medicines, herbal remedies, nutritional supplements, foods, and beverages. However, the existence of even only a few well-documented reports suggests that with greater awareness and more explicit, searching questions by

clinicians, more patients with thrombocytopenia caused by these remedies will be recognized.

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### Conflict of interest

The authors have no conflicts of interest with the topic or data of this manuscript.

### References

1. De Smet PAGM. Herbal remedies. *N Engl J Med* 2002;**347**:2046–56.
2. Molassiotis A, Fernandez-Ortega P, Pud D, *et al.* Use of complementary and alternative medicine in cancer patients: a European survey. *Ann Oncol* 2005;**16**:655–63.
3. Barnes PM, Bloom B, Nahin RL. *Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007*. Hyattsville, MD: National Center for Health Statistics, Center for Disease Control and Prevention, U.S. Department of Health and Human Services, 2008 Dec 10. Report No.: 12.
4. Mainardi T, Kapoor S, Bielory L. Complementary and alternative medicine: herbs, phytochemicals and vitamins and their immunologic effects. *J Allergy Clin Immunol* 2009;**123**:283–94.
5. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med* 2007;**357**:580–7.
6. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis and management. *J Thromb Haemost* 2009;**7**:911–8.
7. Niggemann B, Grüber C. Side-effects of complementary and alternative medicine. *Allergy* 2003;**58**:707–16.
8. Kaufman DW, Kelly JP, Johannes CB, Sandler A, Harmon D, Stolley PD, Shapiro S. Acute thrombocytopenic purpura in relation to the use of drugs. *Blood* 1993;**82**:2714–8.
9. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S, Vondracek T. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998;**129**:886–90.
10. Swisher KK, Li X, Vesely SK, George JN. Drug-induced thrombocytopenia. An updated systematic review, 2008. *Drug Saf* 2009;**32**:85–6.
11. Brvar M, Kozelj G, Mozina M, Bunc M. Acute poisoning with autumn crocus (*Colchicum autumnale*). *Wien Klin Wochenschr* 2004;**116**:205–8.



12. Volcy J, Nzerue CM, Oderinde A, Hewen-Iowe K. Cocaine-induced acute renal failure, hemolysis, and thrombocytopenia mimicking thrombotic thrombocytopenic purpura. *Am J Kidney Dis* 2000;**35**:1–5.
13. Christie DJ, Walker RH, Kolins MD. Quinine-induced thrombocytopenia following intravenous use of heroin. *Arch Intern Med* 1983;**143**:1174.
14. Aubourg P, Adamsbaum C, Lavallard-Rosseau M-C, *et al.* A two-year trial of oleic and erucic acids (“Lorenzo’s Oil”) as treatment for adrenomyeloneuropathy. *N Engl J Med* 1993;**329**:745–52.
15. Lorenzo’s Oil. The Myelin Project 2009 Nov 3. <http://www.myelin.org/en/cms/?293>.
16. Belkin GA. Cocktail purpura an unusual case of quinine sensitivity. *Ann Intern Med* 1967;**66**:583–6.
17. Eisner EV, Korbitz BC. Quinine-induced thrombocytopenic purpura due to an IgM and an IgG antibody. *Transfusion* 1972;**12**:317–21.
18. Korbitz BC, Eisner E. Cocktail purpura. Quinine-dependent thrombocytopenia. *Rocky Mt Med J* 1973;**70**:38–41.
19. Siroty RR. Purpura on the rocks – with a twist. *JAMA* 1976;**235**:2521.
20. Murray JA, Abbott I, Anderson DA, Morgan AD. Bitter lemon purpura. *BMJ* 1979;**2**:1551–2.
21. Brasic JR. Quinine-induced thrombocytopenia in a 64-year-old man who consumed tonic water to relieve nocturnal leg cramps. *Mayo Clin Proc* 2001;**76**:863–4.
22. Caffrey EA, Sladen GE, Isaacs PET, Clark KGA. Thrombocytopenia caused by cow’s milk. *Lancet* 1981;**2**:316.
23. Davies JK, Ahktar N, Ranasinge E. A juicy problem. *Lancet* 2001;**358**:2126.
24. Azuno Y, Yaga K, Sasayama T, Kimoto K. Thrombocytopenia induced by *Jui*, a traditional Chinese herbal medicine. *Lancet* 1999;**354**:304–5.
25. Ohmori T, Nishii K, Hagihara A, Takeda M, Sekido K. Acute thrombocytopenia induced by *Jui*, a traditional herbal medicine. *J Thromb Haemost* 2004;**2**:1479–80.
26. Lavy R. Thrombocytopenic purpura due to *Lupinus termis* bean. *J Allergy Clin Immunol* 1964;**35**:386–8.
27. Arnold J, Ouwehand WH, Smith G, Cohen H. A young woman with petechiae. *Lancet* 1998;**352**:618.
28. Kao WF, Hung DZ, Tsai WJ, Lin KP, Deng JF. Podophyllotoxin intoxication: toxic effect of Bajiaolian in herbal therapeutics. *Hum Exp Toxicol* 1992;**11**:480–7.
29. Lee JJ, Chen HC. Flavonoid-induced acute neuropathy by *Cupressus funebris* Endl (Mourning Cypress). *Am J Kidney Dis* 2006;**48**:e81–5.
30. Squier TL, Madison FW. Thrombocytopenic purpura due to food allergy. *J Allergy* 1937;**8**:143–54.
31. Perrotta S, Nobili B, Rossi F, Criscuolo M, Iolascon A, Pinto D, Passaro I, Cennamo L, Oliva A, Ragione F. Infant hypervitaminosis A causes severe anemia and thrombocytopenia: evidence of a retinol-dependent bone marrow cell growth inhibition. *Blood* 2002;**99**:2017–22.
32. Kojouri K, Vesely SK, George JN. Quinine-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: frequency, clinical features, and long-term outcomes. *Ann Intern Med* 2001;**135**:1047–51.
33. Cerrulli J, Grabe DW, Gauthier I, Malone M, McGoldrick MD. Chromium picolinate toxicity. *Ann Pharmacother* 1998;**32**:428–31.
34. George L, Ioannis E, Radostina T, Antonios M. Severe thrombotic thrombocytopenic purpura (TTP) induced or exacerbated by the immunostimulatory herb *Echinacea*. *Am J Hematol* 2006;**81**:224.
35. Demiroglu YZ, Yeter TT, Boga C, Ozdogu H, Kizilkilic E, Bal N, Tuncer I, Arslan H. Bone marrow necrosis: a rare complication of herbal treatment with *Hypericum perforatum* (St. John’s Wort). *Acta Med* 2005;**48**:91–4.
36. Takahashi Y, Tanaka A, Nakamura T, Fukuwatari T, Shibata K, Shimada N, Ebihara I, Koide H. Nicotinamide suppresses hyperphosphatemia in hemodialysis patients. *Kidney Int* 2004;**65**:1099–104.
37. Raymond RS, Fallon MB, Abrams GA. Oral thymic extract for chronic hepatitis C in patients previously treated with interferon. *Ann Intern Med* 1998;**129**:797–800.
38. Pye KG, Kelsey SM, House IM, Newland AC. Severe dyserythropoiesis and autoimmune thrombocytopenia associated with ingestion of kelp supplements. *Lancet* 1992;**339**:1540.
39. Whitfield MF, Barr DG. Cows’ milk allergy in the syndrome of thrombocytopenia with absent radius. *Arch Dis Child* 1976;**51**:337–43.
40. Jones RH. Congenital thrombocytopenia and milk allergy. *Arch Dis Child* 1977;**52**:744–5.
41. O’Brien T, Silverberg JD, Nguyen TT. Nicotinic acid-induced toxicity associated with cytopenia and decreased levels of thyroxine-binding globulin. *Mayo Clin Proc* 1992;**67**:465–8.
42. Smereck J. Aplastic anemia: a possible toxic effect of an herbal “colon cleansing” preparation. *J Emerg Med* 2009;**36**:191–3.
43. Roberts HJ. Aspartame-induced thrombocytopenia. *South Med J* 2007;**100**:543.
44. Taylor DM, Walsham N, Taylor SE, Wong L. Use and toxicity of complementary and alternative medicines among emergency department patients. *Emerg Med Australas* 2004;**16**:400–6.
45. Parab S, Kulkarni R, Thatte U. Heavy metals in ‘herbal’ medicines. *Indian J Gastroenterol* 2003;**22**:111–2.
46. Reimund E, Ramos A. Niacin-induced hepatitis and thrombocytopenia after 10 years of niacin use. *J Clin Gastroenterol* 1994;**18**:270–1.
47. Rottemburg JB, Launay-Vacher V, Massard J. Thrombocytopenia induced by nicotinamide in hemodialysis patients. *Kidney Int* 2005;**68**:2911–2.
48. Kiguchi T, Kimura F, Kiiya K, Katayama Y, Harada M. Acute thrombocytopenic purpura after ingestion of Shosaiko-to for hepatitis. *Liver* 2000;**20**:491.
49. Lowenthal MN, Jones IG, Desai M. Aplastic anaemia and optic fundus haemorrhages due to traditional herbal remedies. *J Trop Med Hyg* 1978;**81**:177–9.