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Review

Cinnamon: A systematic review of adverse events

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SUMMARY

Cinnamon, from the genus Cinnamomum and Lauraceae family, has been used as a popular spice for thousands of years around the world. Many studies have shown therapeutic effects of cinnamon including its antimicrobial, antiviral, antifungal, antioxidant, antitumor, antihypertensive, antilipemic, antidiabetic, gastroprotective, and immunomodulatory effects. Due to popular use of cinnamon and several human reports on adverse events associated with short or long term use of cinnamon, we aimed to systematically review its human reports of adverse event.

Databases including Medline, Scopus, Science Direct, Embase, PubMed Central and Google scholar were searched using the key words "cinnamon" or "cinnamomum" for clinical trials, case reports and case series. Also spontaneous reports about adverse effects of cinnamon were collected from five national and international spontaneous reporting schemes.

Thirty eight clinical trials were found, five of them reported adverse events. Twenty case reports and seven case series, as well as, spontaneous reports including 160 adverse events were also included. The most frequent adverse events were gastrointestinal disorders and allergic reactions which were self-limiting in the majority of cases.

The available data suggests that despite the safety of cinnamon use as a spice and/or flavoring agent, its use may be associated with significant adverse effects in medicinal uses with larger doses or longer duration of use and should be clinically monitored.

1. Introduction

For thousands of years cinnamon has been used as a popular spice used by different cultures around the world. It is a plant of the laurel Lauraceae family [1]. *Cinnamomum zeylanicum*, *Cinnamomum loureirii*, *Cinnamomum burmanni*, and *Cinnamomum aromaticum* are the four most frequently used species in this family [2]. Cinnamomum is obtained from the inner bark of trees from the genus Cinnamomum [3].

Cinnamon has been widely used in traditional Chinese, Indian, Persian, and Unani medicine for a long time. It is used for several conditions such as; flatulence, amenorrhea, diarrhea, toothache, fever, leukorrhea, common cold and headache [2,4]. This herbal supplement was also traditionally recommended for treatment of impotency, frigidity, dyspnea, eye inflammation, vaginitis, cough, rheumatism, and neuralgia, as well as cardiovascular diseases [5]. Several scientific investigations have shown promising results on many therapeutic effects of cinnamon including its antimicrobial, antiviral, antifungal, antioxidant, antitumor, antihypertensive, antilipemic, antidiabetic, gastroprotective, and immunomodulatory effects [6–9].

Pharmaceutical analyses of its essential oil revealed that cinnamaldehyde and *trans*-cinnamaldehyde are the major elements of cinnamon [10]. Procyanidins and catechins are also found in cinnamon bark [11]. Some investigators linked the beneficial effects of cinnamon ingredients to activation of peroxisome proliferator-activator [12].

Despite advances in biomedicine, plants still play an important role in human health care. Medicinal plants are becoming more

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List of abbreviations

AEs	adverse events
NM	not mentioned
C.b	*Cinnamomum burmannii*
C.c	*Cinnamomum cassia*
C.z	*Cinnamonum zylanicum*
F	female
M	male
CAD	coronary artery disease
DM 2	Diabetes mellitus type 2
HTN	hypertension
HLP	hyperlipidemia
NAFLD	Non-alcoholic fatty liver disease
PCOS	polycystic ovarian syndrome

popular and integrated into medical care for many chronic diseases [13–15]. Contrary to popular beliefs, herbal medicines are not completely safe and may have adverse effects for instance; organ toxicity, allergic contact dermatitis, and herbal and drug interactions [16,17].

Despite several reports on drug interactions and adverse events associated with short or long term use of cinnamon, there is no systematic review on this topic. Hence, we aimed to collect safety data from human studies on mono-preparations of cinnamon, as a systematic review.

2. Methodology

A comprehensive systematic literature search was carried out in March 2016 using these electronic databases: Medline, Scopus, Science Direct, Embase, Pubmed Central and Google scholar. The search terms were "cinnamon" or "cinnamomum" in subject, abstract and keywords. The literature search was confined to articles in the English language. Moreover, spontaneous reports about adverse effects of cinnamon were requested from the following database: WHO Collaborating Centre for International Drug Monitoring Database, UK Medicines Control Agency, US Food and Drug Administration Office of Special Nutritionals, Australian Database of Adverse Event Notifications (DAEN), Canada Vigilance Adverse Reaction Online Database, and German Bundesinstitut Fur Arzneimittel Und Medizinprodukte (BfArM). The reference lists of all eligible articles were searched for other potentially eligible studies.

All data from clinical trials, case reports, case series, and spontaneous reporting schemes were included in this review. Only human studies assessing mono-preparations of cinnamon were included. Data from cinnamon in combination with other herbs, its homeopathic preparations, as well as animal and *in vitro* investigations were excluded (Fig. 1).

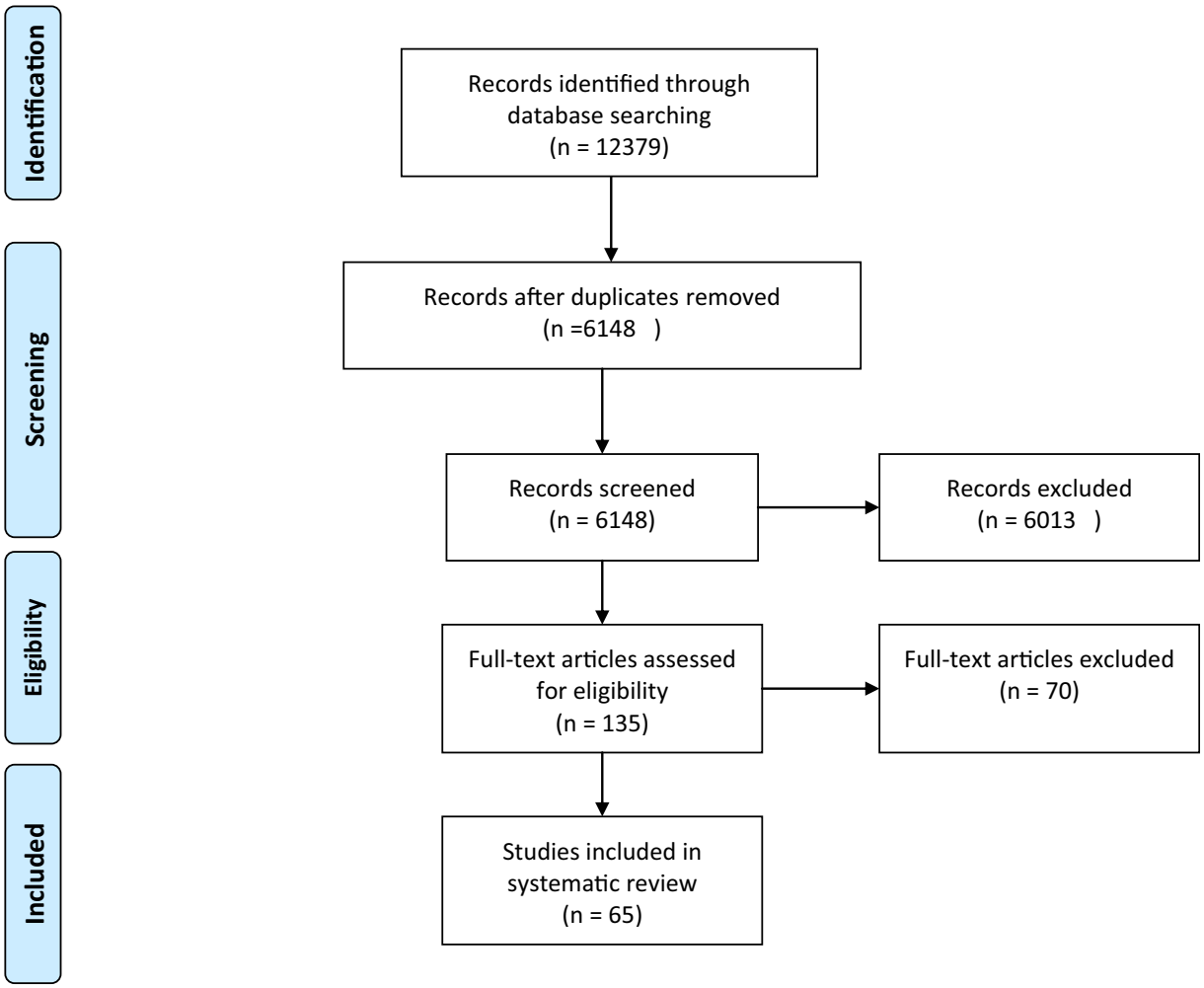

Fig. 1. PRISMA flow diagram of the study.

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All the obtained information were read and evaluated by one reviewer and separately checked by at least one independent author. In the case of duplicated reports, only the paper which was in more details was enrolled in the study. The papers were screened by checking the title and the abstract and those which were related to our study were undergone for further assessments. Then, the full text articles were reviewed for eligibility.

Data were extracted based on predefined protocol (including: study population, duration of use, used preparation, dose of use, and number and type of reported adverse events). Two independent reviewers extracted the data and the results were checked, compared and edited by the third reviewer. No formal assessment of the statistics of the primary data was made.

3. Result

3.1. Clinical trials

Thirty eight clinical trial were included in this review. Among them 5 studies reported adverse events [18–22], 14 reported no adverse events [7,23–35], and 19 trials did not mention anything about side effects [12,36–53].

3.1.1. Randomized controlled trials reporting adverse effects

Among five randomized controlled trials that had reported adverse event on cinnamon (see Table 1), two studies had evaluated the effect of cinnamon in diabetic patients [19,20], one on women with poly cystic ovary syndrome [21], another study was on patient with positive Campylobacter urease test [18], and the last was on seasonal allergic patients [22]. In these five studies *Cinnamomum cassia* was used in two studies [20,21], and *Cinnamomum zylanicum* in one study [22]. The other two reports did not indicate the species of cinnamon [18,19].

In these studies, a total of 141 people were allocated to the cinnamon groups and 17 of them had experienced adverse effects. The most common adverse effects were gastrointestinal problems in nine patients (stomachache, nausea, constipation and heart burn) [18,21]. Four patients had reported headache [21], two patients had reported dermatological problems (hives and rash) [19,20] and finally, two patients had reported menstrual cramps [21]. Also in seasonal allergic patients cough, fever, headache, body aches, and throat irritation were reported in seven patients after cinnamon consumption [22].

The shortest treatment period was four weeks (2 studies) [18,22], and the longest period was six months (one study) [21]. The other two studies were 90 days [19,20]. The minimum daily dose was 200 μg in the form of nasal spray [22], minimum and maximum daily dose which was consumed orally was 80 mg and 1.5 g [16,18].

3.1.2. Randomized controlled trials reporting no adverse effect

Fourteen randomized controlled trials had stated no adverse effect in their reports [7,23–35]. Total of 488 patients were involved in the cinnamon groups. Diabetes mellitus was the most prevalent condition among patients in these studies (7 reports with 254 patients) [23,24,26–29,34]. *Cinnamomum cassia* species was used in five studies [23,24,26,34,54], and *Cinnamomum zylanicum* in seven of them [7,27,29–33]. However, two studies did not mention the species of cinnamon [25,28]. The used dosage ranged from 456 mg [54] to daily dose of 6 gr [28]. Three studies reported single dose of cinnamon [7,32,33]. Also, longest period of intervention was four months [23,54] (see Table 2).

3.1.3. Randomized controlled trials not mentioning adverse effect

Nineteen studies with 353 subjects had not mentioned anything about adverse effect in their reports [12,36–53]. Due to wide-range of potential usage of cinnamon, study populations included healthy volunteers (9 studies) [38,39,41–43,45,46,51,53], patients with diabetes mellitus type 2 (7 studies) [12,36,37,40,47,49,52], or impaired glucose tolerance (2 studies) [44,48], and non-alcoholic fatty liver disease (1 study) [50]. *Cinnamomum cassia* was also the most popular species in these studies (12 reports) [12,36–38,40,42–44,46,47,49,53]. The minimum daily dose was 100 mg [39] and maximum daily dose was 60 g in a single dose [51]. Duration of intervention ranged from one day (8 studies) [38,41,42,45,46,48,51,53] to three months (1 studies) [40] (see Table 3).

3.2. Case reports/series

3.2.1. Case reports

This systematic review included 20 case report studies including 13 women and seven men ranging from 11 to 74 years of age (Table 4) [55–74]. Chewing gum was the most common method of exposure, reported in 8 cases [57,63,67–71,73], and then topical exposure to cinnamon oil was reported in six cases [55,58,61,64,65,72]. Other exposure methods were as supplements or flavoring agents. All cases were healthy before the exposure except three of them (one with diabetes mellitus, another with hypertension and rheumatism and the last one with coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia, and depression) [55,60,74]. The most common adverse effect was dermatitis which was reported in eight studies [58,59,61,62,64,66,71,72], followed by stomatitis in five studies [56,57,68,70,73]. Other reported adverse reactions in case

Table 1
Placebo-controlled trials of cinnamon mono preparations reporting adverse events (AEs).

Trial	n	Patient population	Preparation, daily dose, species	Treatment duration	AEs in Cinnamon group (Number)	AEs in control group
Nir et al. [18]	15	Patient with positive Campylobacter urease test	Ethanol extract of cinnamon, 80 mg, NM	4 weeks	Stomach ache (2), nausea (3), constipation (1)	–
Altschuler et al. [14]	28	Diabetes mellitus type 1	Powder (pill), 1 gr, NM	90 days	Hypoglycemic seizure (1) Hives (1)	Stomach aches (1) Frequent illnesses (1)
Crawford [15]	55	Diabetes mellitus type 2	Powder (cap), 1 gr, C.c	90 days	Rash (1)	–
Kort and Lobo [16]	23	Female with polycystic ovarian syndrome	Powder (cap), 1.5 gr, C.c	6 months	Headache (4), heartburn symptoms (2), menstrual cramps (2), nausea with diarrhea (1)	–
Walanj et al. [17]	20	Seasonal allergic rhinitis patients	Nasal spray, 200 μg/200 L, C.z	4 weeks	Cough, fever, headache, bodyaches, and throat irritation (7)	Cold, earache, fatigue, itching in eyes, throat irritation and watery eyes (8)

n: number of patients in cinnamon group, AEs: adverse events, NM: not mentioned, C.c: *Cinnamomum cassia*, C.z: *Cinnamonum zylanicum*.

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Table 2
Placebo-controlled trials of cinnamon mono preparations reporting no adverse events (AEs).

Trial	N	Patient population	Preparation, daily dose, species	Treatment duration	Comment
Mang et al. [23]	33	DM 2	Powder (cap), 3 gr, C.c	4 months	No adverse effects were observed
Suppapitiporn et al. [24]	20	DM 2	Powder (cap), 1.5 gr, C.c	12 weeks	No adverse effects were reported
Wang et al. [25]	7	PCOS	Powder (cap), 1 gr, NM	8 weeks	There were no reported side effects in either study
Akilen et al. [26]	30	DM 2	Powder (cap), 2 gr, C.c	12 weeks	No side effects were reported because of cinnamon intervention
Vafa et al. [27]	22	DM2	Powder (cap), 3 gr, C.z	8 weeks	No adverse effects
Sharma et al. [28]	50	DM 2	Powder (cap), 6.3 gr, NM	12 weeks	No adverse effects were observed in the study
Azimi et al. [29]	50	DM2	Glasses of black tea with 3 g cinnamon, 3 gr, C.z	8 weeks	No adverse reactions caused by the use of the herbal medicines
Beejmohun et al. [7]	18	Healthy	Powder (cap), 1 gr, C.z	1 day	No side effects were reported during the study
Mohammadi et al. [30]	72	Women after episiotomy	Ointment, 4 ml (4 gr), C.z	10 days	No side effects were reported by the participants in either group
Gupta and Jain [31]	35	Healthy	Mouth wash, 10 ml (1 gr), C.z	30 days	There were no reports of adverse reactions to any of the mouth rinses used
Jaafarpour et al. [32]	38	Female with dysmenorrhea	Powder (cap), 2.5 gr, C.z	1 day	No side effects were found with this dose of cinnamon
Jaafarpour et al. [33]	38	Female with dysmenorrhea	Powder (cap), 2.5 gr, C.z	1 day	No side effects were found with this dose of cinnamon
Tangvarasittichai et al. [34]	49	DM 2	Powder (cap), 1.5 gr, C.c	60 days	Without any adverse events
Liu et al. [54]	26	Overweight or obese pre-diabetic	Powder (cap), 456 mg, C.c	4 months	None of the serious adverse events was considered to be related to the study treatment

n: number of patients in cinnamon group, NM: not mentioned, C.c: *Cinnamomum cassia*, C.z: *Cinnamonum zylanicum*, DM 2: Diabetes mellitus type 2, PCOS: polycystic ovarian syndrome.

reports were acute hepatitis, exacerbation of rosacea, erythema multiform-like sensitivity reaction, cheilitis, mucositis, and squamous cell carcinoma. All the complications had disappeared in all the mentioned studies (17 studies, 5 with intervention [58,59,63,72,74] and 12 without any intervention [56,57,60–62,66–71,73]).

3.2.2. Case series

This systematic review includes 7 case series (1976–2015) with total subjects of 116 (74 women and 42 men) ranging from 16 to 80 years of age (Table 5) [64,75–81]. All cases were healthy except for one with obesity and fibromyalgia [75]. Dermatitis (3 studies) [75,76,80] and stomatitis (2 studies) [77,81] were the most common reported reactions. Almost all cases were asymptomatic after the elimination of cinnamon.

3.3. Spontaneous reporting schemes

3.3.1. World health organization report

World Health Organization (WHO) collaborating center for International Drug Monitoring Database has registered 44 spontaneous adverse reports to mono-preparations of cinnamon from 1973 to June 2016. Most cases were reported in the United States, which belonged to 18–44 years age group and had equal sex ratio (22/22). Gastrointestinal disorders were the most frequent type of complications. The detailed information on the adverse events of

Table 3
Placebo-controlled trials of cinnamon mono preparations in which nothing were reported about adverse events.

Trial	N	Patient population	Preparation, daily dose, species	Treatment duration
Khan et al. [31]	30	DM 2	Powder (cap), 1, 3, 6 gr, C.c	40 days
Vanschoonbeek et al. [32]	12	Postmenopausal women diagnosed with DM 2	Powder (cap), 1.5 gr, C.c	6 weeks
Solomon and Blannin [33]	7	Healthy men	Powder, 5 gr, C.c	1 day
Ranjbar et al. [34]	18	Healthy subjects	Drink cinnamon (100 mg in 300 ml tea), 100 mg, C.z	10 days
Blevins et al. [35]	29	DM 2	Powder (cap), 1 gr, C.c	3 months
Hlebowicz et al. [36]	14	Healthy subjects	Powder (with rice), 6 gr, NM	1 day
Hlebowicz et al. [37]	15	Healthy subjects	Powder, 1, 3 gr, C.c	1 day
Solomon and Blannin [38]	15	Healthy men	Powder (pill), 3 gr, C.c	14 days
Roussel et al. [39]	11	People with impaired fasting glucose that are overweight or obese	Dried aqueous extract of cinnamon (cap), 500 mg, C.c	12 weeks
Mettler et al. [40]	27	Healthy subjects	Powder (with meal), 4 gr, C.c	1 day
Markey et al. [41]	9	Healthy subjects	Powder (cap), 3 gr, C.z	1 day
Wainstein et al. [10]	29	DM 2	Powder (cap), 1200 mg, C.c	12 weeks
Abraham et al. [42]	24	Healthy subjects	Powder, 2 gr, C.c	1 day
Hoehn and Stockert [43]	9	DM 2	Powder (cap), 1 gr, C.c	9 weeks
Wickenbere et al. [44]	10	Subjects with impaired glucose tolerance	Powder (cap), 6 gr. C.z	1 day
Hasanzade et al. [45]	35	DM2	Powder (cap), 2 gr, C.c	60 days
Askari et al. [46]	23	NAFLD	Powder (cap), 1.5 gr, NM	12 weeks
Bernardo et al. [47]	15	Non diabetic adult	Tea, 60 gr, C.b	1 day
Whitfield et al. [48]	12	DM 2	Powder (in honey), 4.5 gr, NM	40 days

n: number of patients in cinnamon group, NM: not mentioned, C.c: *Cinnamomum cassia*, C.z: *Cinnamonum zylanicum*, C.b: *Cinnamomum burmannii*, DM 2: Diabetes mellitus type 2, NAFLD: Non-alcoholic fatty liver disease.

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Table 4
Adverse events of cinnamon reported in case reports.

Study	Age and sex	Condition	Exposure	Adverse event (s)	Outcome
Brancheau et al., 2015 [74]	73 F	CAD, HTN, DM, HLP, depression	Cinnamon supplements for 1 week	Acute Hepatitis (tender abdomen, with palpation more prominent in the epigastric region and right upper quadrant, positive Murphy's sign, but no scleral icterus.)	As her hospital course progressed, her abdominal pain slowly resolved and she was discharged home.
Biron et al., 2013 [73]	25 F	Healthy subjects	Cinnamon-flavored gum	Oral contact stomatitis (bilateral white/yellowish nonwipeable lesions on the lateral aspects of the tongue that extended onto the dorsal surface)	Over a several day period that she stopped chewing the gum, a gradual reduction of the lesion was revealed 2 days later with complete resolution by the fourth day.
Lauriola et al., 2010 [72]	18 F	Healthy subjects	The galenic vaginal suppositories contained cinnamon oil (3%)	Allergic contact dermatitis (Two symmetrical erythematoedematous patches on the glutei, leading to an acute eczema. Erythematous vulvitis and thick leucorrhea were also present)	The dermatitis healed following treatment with oral antihistamines, systemic and topical steroids
Georgakopoulou 2010 [71]	20 F	Healthy subjects	Cinnamon gums	Contact dermatitis (white elevated mucosal patches in the right lateral board of her tongue)	She had a normal tongue appearance seven days after completely avoidance of the use of cinnamon flavored chewing gums
Kind et al., 2010 [70]	39 F	Healthy subjects	Cinnamon flavored chewing gums	Allergic contact stomatitis (Bilaterally on the buccal mucosa, white plaques with a verrucous surface and a surrounding erythema, but soft on palpation, were present)	After omission of the chewing gums, there was no recurrence
Siqueira et al., 2009 [69]	53 M	Healthy subjects	Cinnamon-flavored chewing gum	Intraoral contact mucositis. bilateral white plaques that could not be scraped off overlying buccal mucosa	After the patient was advised to discontinue use of the irritant agent, lesions healed completely in a week
Tremblay and Avon 2008 [68]	42 F	Healthy subjects	Cinnamon-flavored chewing gum	Allergic contact stomatitis (In the left buccal mucosa, a white and red partially erosive lesion with a traumatic appearance was observed beginning in the retrocommissural area and extending to the pterygomaxillary raphe.)	After use of cinnamon-flavored chewing gum was discontinued, the lesions of the buccal mucosa disappeared completely
Campbell et al., 2008 [55]	68 F	DM 2	Cinnamon oil pills for 2 weeks	Acute exacerbation of her rosacea	
Nadiminti et al., 2005 [56]	37 F	Healthy subjects	Cinnamon-flavored breath mints	Allergic contact stomatitis (oral erosions clustered on the left and right buccal surfaces, an aphthous ulcer on the tongue and gingival erythema)	Discontinuation of exposure to the offending mints led to cessation of lesion development
Bousquet et al., 2005 [57]	34 F	Healthy subjects	Cinnamon gum	Recurrent stomatitis for 1.5 years, (lichen like lesions of the oral mucosa of cheeks and lateral borders of the tongue)	Remained for a few weeks after she returned, and disappeared without any treatment
Garcia-Abujeta et al., 2005 [58]	74 F	Healthy subjects	Mud bath with cinnamon essential oil in a spa	Contact dermatitis (extensive eczematous and bullous dermatitis affecting exposed areas (arms and legs) with desquamation and residual hyperpigmentation)	The patient was referred to another hospital in which she received steroid treatment. A significant improvement was achieved after avoiding confectionery products and cola drinks
Hartmann and Hunzelmann 2004 [59]	47 M	Healthy subjects	Cinnamon as an odor neutralizing agent in shoe insoles	Allergic contact dermatitis (vesicular dermatitis on both soles consistent with a clinical diagnosis of podopompholyx)	Treatment with topical corticosteroids initially failed to clear the skin lesions. He had developed erysipelas on the left foot 5 days after the onset of the eczema and was therefore hospitalized and treated with intravenous antibiotics in addition to topical corticosteroids. Within 2 weeks of this treatment, marked improvement of the eczema

(*continued on next page*)

Table 4 (*continued*)

Study	Age and sex	Condition	Exposure	Adverse event (s)	Outcome
					and clearance of the erysipelas were achieved
Donald and Cohen 2000 [60]	66 F	HTN, rheumatism	Cinnamon-flavored bread pudding, cinnamon-flavored sugar on bread and rolls, herbal tea with cinnamon	Cinnamon-induced oral erythema multiform like sensitivity reaction (large areas of serpiginous ulcerations on the labial and buccal mucosa and on the ventral surface of the tongue, as well as that her lips were swollen)	The patient was treated repeatedly with topical and systemic steroids but responded to them only temporarily. The patient was cured when cinnamon was eliminated from her diet
Sanchez-Perez and Garcia-Diez 1999 [61]	32 M	Healthy subjects	Oil of cinnamon as a component of "Balsam from ash extract" cream	Occupational allergic contact dermatitis (pruriginous, vesicular, erythematosquamous plaques and fissures on all fingers and both palms)	Stopping the use of this cream led to improvement within 2 days
De Benito V and Alzaga 1999 [62]	52 M	Healthy subjects	Chinese cinnamon as a flavoring agent in coffee	Occupational allergic contact dermatitis (hand eczema)	The patient recovered after he was advised to avoid contact with cassia and is still asymptomatic and working
Westra et al., 1998 [63]	24 F	Healthy subjects	Cinnamon-flavored gum (up to five packs every day)	Squamous cell carcinoma of the tongue. A 0.8-cm ulcer was noted along the right lateral border of the mobile tongue. Adjacent to the ulcer was a 0.5-cm patch of leukoplakia	Ulcers were removed by surgery without complications and she is closely followed for recurrent disease and no longer chews gum
Nixon 1995 [64]	50 M	Healthy subjects	Oil of cinnamon (baking pastries and cakes)	Allergic contact dermatitis of hands (rash which began on both palms of his hands and then spread to the dorsum of his right hand, itching, which was worse at night and at work)	
Sparks 1985 [65]	11 M	Healthy subjects	Cinnamon oil	Cinnamon Oil Burn (10 by 12 cm second degree burn on his posterior thigh surrounded by a 3–4 cm first degree burn. It is as a result of cinnamon oil spill from a broken vial in his rear pants pocket)	
Farkas 1981 [66]	35M	Healthy subjects	Boiled wine or rice pap seasoned with cinnamon	Perioral dermatitis	On a diet without cinnamon the eruption cleared within 10 days
Miller 1941 [67]	25 F	Healthy subjects	Oil of cinnamon present in bubble gum	Cheilitis (swelling and mild erythema about the lips)	Complete amelioration of symptoms followed avoidance of the oil of cinnamon

F: female, M: male, DM 2: diabetes mellitus type 2, CAD: coronary artery disease, HTN: Hypertension, HLP: hyper lipidemia.

cinnamon reported to WHO are summarized in Supplementary file 1.

3.3.2. UK Medicines Control Agency

From July 1963 to Oct 2015, the UK Medicines Control Agency had received reports of 58 adverse events with cinnamon in 21 patients, including one fatal outcome that resulted from hepatic failure. No information regarding other suspected drugs or causality was available. Nervous system disorders (including headache, amnesia, dizziness and burning sensation) were the most frequent type of complications (Supplementary file 2).

3.3.3. US food and Drug Administration Office

This is the most updated report (June 2016) of the Special Nutritionals Adverse Event Monitoring System included 91 reports associated with the consumption of cinnamon mono-preparations. Gastrointestinal disorders were the most prevalent reported complications (Supplementary file 3).

3.3.4. Other spontaneous reporting schemes

Other spontaneous reporting schemes including Australian Database of Adverse Event Notifications (DAEN), Canadian Vigilance Adverse Reaction Online Database and German Bundesinstitut Fur Arzneimittel Und Medizinprodukte (BfArM) had reported total of 11 adverse events reported in six cases having used cinnamon mono-preparations with no fatal outcomes (Supplementary file 4).

4. Discussion

Cinnamon is a medicinal plant which is used as a dietary supplement for a wide range of diseases. Also, multiple preclinical and clinical studies have examined efficacy of cinnamon in these medical conditions. Diabetes mellitus is the most popular investigated indication for cinnamon. Despite conflicting results, many studies showed improvement in glycemic control in patients with diabetes and pre-diabetes taking cinnamon supplementation [82]. Systematic reviews also demonstrated that cinnamon supplementation can reduce blood triglycerides and total cholesterol. However, no significant effect on low and high density lipoprotein cholesterols was reported [83]. Multiple studies also supported beneficial effects of cinnamon on metabolic syndrome [84].

Even though there are multiple systematic reviews on the efficacy of different types of cinnamon supplementation in human

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Table 5
Adverse events of cinnamon reported in case series.

Study	n	Age and sex	Condition	Exposure	Adverse event (s)	Outcome
Renton et al., 2015 [75]	3	2 F (62,73), 1 M (16)	2 Healthy subject, 1 with obesity and fibromyalgia	Cinnamon flavoring agents, breathe freshening strips, toothpaste. apple dipped in cinnamon	Intraoral allergic contact dermatitis	After discontinuing the use, symptoms in 1st patient never returned, in 2nd patient 90% improvement, in 3rd patient resolved within 3 weeks
Ackermann 2009 [76]	6	3 F, 3 M 30–61 y/o	Healthy	Workers handling foods (Baker or restaurant worker)	Occupational allergic contact dermatitis	During the periods when they were not working, the eczema healed completely
Endo and Rees 2007 [77]	37	5 M, 32 F 20–80 y/o (mean 48.4 ± 15.2)	NM	Cinnamon flavoring agents (toothpaste, foods and chewing gum) for 1–2 weeks	Contact stomatitis. Orofacial granulomatosis	Signs and symptoms subsided after discontinuing the use of the agents
Miller et al., 1992 [81]	14	7 F, 7 M 37–73 y/o	Healthy subjects	Gum (10), Candy (2), Antacid (1), Breath savers (1), Tooth plast (1), stick bark (1)	Stomatitis venenata	Almost all had 100% resolution
Allen and Blozis 1988 [78]	10	8 F, 2 M 30–60 y/o	Healthy subjects	Cinnamon-flavored chewing gum	Oral mucosal reactions. (erythematous patches with varying degrees of superimposed keratosis or ulceration, or both and confined to the buccal mucosa and lateral border of the tongue)	Symptoms typically resolved within 1–2 days of discontinuing the product containing cinnamon
Uragoda 1984 [79]	40	21 F, 19 M 18–53 y/o (mean 31.8)	Healthy subjects	In the industry that was processing cinnamon before export (average of four years' service)	Symptoms (87.5%), asthma (22.5%). irritation of skin (50%), loss of hair (37.5%), smarting of eyes while at work (22.5%). Loss of weight (65%) was the commonest finding	NM
Calnan 1976 [80]	6	5 M, 1 F 32–65 y/o	Not mentioned	Antiseptic ointment containing oil of cinnamon	Allergic contact dermatitis	It was resolved in one patient after stopping the usage, and in another patient rapidly settled with topical steroid therapy. Others were not mentioned

n: number of patients, F: female, M: male, NM: not mentioned.

studies, but its adverse events were never systemically reviewed. Inadequate safety data is a frequent issue with herbal medicines. Additionally, inappropriate perception of the general public on the safety of these drugs due to their natural source is another problem. Evidences show under-reporting of adverse events of herbal drugs in comparison with conventional medicines [85].

In this study multiple reports on adverse events associated with the use of cinnamon mono-preparation in human were reviewed. These include reports from clinical trials, case reports/series and national/international spontaneous reporting schemes.

Most clinical trials neglect to collect information on adverse events. It is mostly because they are designed to assess efficacy rather than safety. In the case of cinnamon among 38 clinical trials, 19 trials had not mentioned anything about potential side effects. Methods on collecting information of adverse events is different and in many cases not accurate enough. However, since clinical trials are controlled, reported events are more accurate in comparison with other methods. Considering these issues, this review has identified 38 clinical trials which showed the exposure of 982 individuals to cinnamon mono-preparation with relatively few adverse effects being reported. The most frequent complaints were self-limiting and gastrointestinal disorders. In most cases no significant differences were observed between the cinnamon and the control groups.

Case reports/series provided more comprehensive information about individual patients. They also provided more indebt information on temporal relationships and the outcome; however, most reports did not identify the species of cinnamon which could be a contributing factor in the reported adverse events. The importance of this issue becomes more evident when it is understood that different species of cinnamon have different levels of toxic ingredients. For example coumarin, as the most important hepatotoxic substance of cinnamon, has different levels ranging from less than 0.01 g/kg in *Cinnamomum verum* to 3.6 g/kg in *Cassia Cinnamon* [86]. Different types of allergic reactions are the most common types of these reports which were self-limiting in the majority of cases.

The data obtained from spontaneous reporting schemes was conducted on a large population; however, the rate of side-effects remained unclear in their reports, due to lack of information on the total users population. Causality is the next important limitation in the interpretation of information derived from spontaneous reporting schemes.

Moreover, the claim on interaction between the use of herbal products and subsequent adverse events are more challenging than such a claim on pharmaceutical products. Different types of contamination, mislabeling and routine usage of compound are the main sources of this uncertainty. It is possible that there is some overlap between the data from the various reported schemes. Thus, the outcomes of adverse events were not available in all databases; however, the existing information suggests that most of them were minor and reversible.

System standardization of adverse events associated with herbal products is necessary in order to improve safety evaluation. These reports should include exact identification, any available chemical profile, the dose and duration of treatment as well as assessment. In addition to standardization of data gathering methods, the spontaneous reporting schemes should be more introduced to the users of herbal medicines in developing countries. Even though there is a huge population who use traditional

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medicine in Asia and Africa [87], no comprehensive information is available on spontaneous reporting schemes.

In conclusion, the available data suggests that cinnamon is safe to be used in routine diet as spice and/or flavoring agent. It is also well tolerated in controlled clinical settings. However, its use for medicinal purposes, in large doses or long durations, may lead to some adverse effects and it should be clinically monitored. The most significant adverse events are stated in case reports with limited causality assessment. Reports from clinical trials were also mostly minor and self-limiting.

Conflict of interest

All of the authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.03.013.

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