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Research Article

The Safety of Cruciferous Plants in Humans: A Systematic Review

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Some cruciferous plants may serve as preventive treatments for several medical conditions; our objective was to systematically investigate their safety in humans. Four electronic databases were searched, and, of 10,831 references identified, 50 were included. Data were extracted by two independent reviewers, whereafter the association between interventions and adverse events was assessed. Adverse events in 53 subjects were identified through clinical trials; of these, altered drug metabolism was rated as certainly/likely caused by cruciferous plants. Adverse events in 1247 subjects were identified through observational studies, of which none received high causality ratings. Adverse events in 35 subjects were identified through case reports, of which allergies and warfarin resistance were rated as certainly/likely caused by cruciferous plants. We conclude that cruciferous plants are safe in humans, with the exception of allergies. Individuals treated with warfarin should consult their physician. Further investigation of uses of cruciferous plants in preventative medicine is warranted.

1. Introduction

In the last decade, a rapid rise in the demand for natural health products has become evident. This prominent trend stems from increasing awareness of the potential for significant adverse effects caused by pharmacologic interventions, along with a growing interest in preventive medicine strategies [1].

A group of plants that has been shown to possess strong anti-inflammatory and antioxidative abilities is the cruciferous plants of the *Brassica* genus. Brassica is a genus of plants in the Brassicaceae family. Vegetables of the family Brassicaceae (also called Cruciferae) are generally referred to as cruciferous vegetables. These vegetables are widely cultivated, with many genera, species, and cultivars being raised for food production. The most common Brassica vegetables eaten by people are in a single species (*B. oleracea*), including kale, collard greens, cabbage, Brussels sprouts, kohlrabi, broccoli, and cauliflower. Numerous other species in the genus are also edible such as mustard (*B. nigra*), Chinese cabbage (*B. rapa*), and oilseed rape (*B. napus;* sometimes referred to as "rapeseed oil" or "canola") [2].

Some members of this group have received wide acclaim as potential natural preventers or attenuators of several health conditions such as coronary artery disease, gastritis, and cancer [3–8]. Recent studies reveal that these therapeutic effects may extend to the fetus as well: an international case-control study showed that maternal consumption of cruciferous vegetables during pregnancy decreases the risk of childhood anaplastic astrocarcinomas [9]; a study in rats found that offspring of spontaneously hypertensive rats that consumed broccoli sprouts during gestation had lower blood pressure and reduced markers of oxidative stress and inflammation, compared to controls [10].

The impetus for this systematic review stems from work done in our laboratory that has shown the potential benefit of supplementing the diet of pregnant dams with broccoli sprouts in preventing perinatal brain injury. In this regard,

Table 1: Eligibility criteria and data extracted[1].

PICOS	Eligibility criteria	Data extracted
Patient	All human subjects were included	Age, concurrent medical conditions and treatments, reason for intervention (where relevant)
Intervention	All types of exposure (oral, topical, or respiratory) to cruciferous plants, their derivatives, or their constituents	Plant or substance exposed to, route of exposure, duration of exposure, dose (if available)
Comparators	Reports with or without a comparator group. Reports without control groups were included in order to include all potential adverse events	Numbers in the intervention and comparator groups (when relevant)
Outcome	Reports of presence or absence of adverse events	Presence or absence of adverse events, description of adverse event, acute management of adverse event (for case reports), outcome (when available), and causality
Study design	All study designs which were relevant to the assessment of safety were included. Studies in all languages were included and translated when necessary	Type of study design and setting

[1] PICOS: patient, intervention, comparators, outcome, study design.

we have established a model of chronic placental insufficiency that results in fetal growth restriction and damage to the white matter of the brain, reminiscent of periventricular leukomalacia, the anatomic hallmark of cerebral palsy. Supplementing the maternal diet during the last trimester of pregnancy and first weeks of infant nutrition prevented the white matter injury and accompanying behavioural deficits in the offspring. These findings suggest, for the first time, a safe and efficacious approach to the prevention of developmental disability and cerebral palsy [11]. In order to provide the background in which to determine whether this therapy would be acceptable for humans, a thorough determination of the safety of the cruciferous species of plants in humans is necessary.

Researchers now believe that the key to the therapeutic abilities of cruciferous plants is their high content of phase-2 enzyme inducers such as sulforaphane, which induce the transcription of genes found under the control of the antioxidant response element (ARE). This causes an upregulation of the endogenous antioxidant glutathione, crucial to the cell's ability to withstand oxidative stress [12–14].

Several reviews evaluated the safety and health benefits of some components of cruciferous plants, such as indole-3-carbinol and isothiocyanates, and found them safe for humans [15, 16]. However, to our knowledge, a systematic review evaluating the safety of cruciferous plants, namely, the degree of certainty that they would not cause any adverse effects, has not yet been published.

The purpose of this paper is to systematically collect and synthesize all published reports of human adverse events associated with exposure to cruciferous plants. This approach of analyzing safety of a multi-ingredient natural product is especially important when considering consumption of the whole plant as a therapeutic means, as opposed to treatment with an isolated component or metabolite of a plant.

2. Methods

This systematic paper was undertaken in line with the relevant criteria of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [17]. The following methods used in the systematic review, including identification, screening, eligibility criteria, inclusion, and data extraction, were agreed upon by the authors *a priori*.

References were identified through comprehensive search strategies, which were developed in conjunction with a research librarian. An electronic search of the following four databases was performed: Medline, Embase, Pascal, and IPA (International Pharmaceutical Abstracts), from inception to July 2010, irrespective of language. The following search terms were used: isothiocyanate, Brassica, cruciferous, glucoraphanin, sulforaphane, broccoli, kale, cabbage, cauliflower, collard green, Brussels sprout. MESH headings and keywords were searched, and truncation was used as needed. A list of the search strategies is available as supplemental material available online at doi: 10.1155/2012/503241.

The research question and eligibility criteria were developed by using PICOS (patient, intervention, comparators, outcome, study design). The inclusion criteria were any studies reporting original data, addressing safety of cruciferous plants, their derivatives, or their constituents, to humans. Details of the eligibility criteria are reported in Table 1.

The references were imported into a bibliographic database (RefWorks). Titles and abstracts of identified studies were independently screened by two reviewers. Full texts for potentially relevant studies were obtained and reviewed for inclusion based on predetermined criteria. Disagreement was resolved by consensus, and if necessary a third party was consulted (JYY).

Data was extracted by two independent reviewers, using standardized forms. Disagreement was resolved by consensus. Data relating to the patient or group, the intervention,

the comparator group (where relevant), the outcomes measured (adverse events or lack thereof), and the study design were extracted as detailed in Table 1.

The degree of association between the intervention and the adverse event was independently assessed by the two reviewers using the Causality Algorithm used by Health Canada and the WHO Collaborating Centre for International Drug Monitoring (Health Canada 2009). Categories for assessment were certainly, likely, possibly, unlikely, conditional/unclassified, and Unassessible/Unclassifiable. Disagreement between reviewers was resolved by discussion. Guidelines used to assess causality are available as supplemental material.

The studies were finally categorized into 3 groups: (1) trials, (2) observational studies, and (3) case reports. Studies were classified as controlled clinical trials when involving one or more test treatments, at least one control treatment, specified outcome measures for evaluating the studied intervention, and when the method for assigning patients to the test treatment was not a mathematical randomization technique. Randomized controlled trials, on the other hand, were defined as studies in which randomization using mathematical techniques, such as the use of a random numbers table, is employed to assign patients to test or control treatments. Studies were classified as single-case experimental design trials when the subjects served as his/her own control, rather than using another individual or a group.

We did not perform a meta-analysis as the inclusion criteria for subjects, interventions, clinical outcomes, and study designs were very heterogeneous; conducting a meta-analysis using these data would not have been appropriate.

3. Results

3.1. Study Characteristics. Searches resulted in a total of 10,831 references. After screening of titles and abstracts, the full texts of 367 articles were obtained. Of these, 50 articles met all inclusion criteria. Of the total included publications, 45 were published in English, 2 were published in German, and one each was published in Italian, French, and Spanish.

Articles were excluded for the following reasons: not human subjects (210), not evaluating adverse effects or lack thereof (21), intervention or substance exposure does not include cruciferous plants (2), not presenting original data (47). Thirty-seven articles discussing toxic oil syndrome (37) were excluded post hoc for reasons presented below.

Of the 50 included studies, 13 were trials (6 single-case experimental design trials, 4 controlled clinical trials, and 3 randomized control trials (RCTs)), 13 were observational studies (7 cohort studies, 3 case-control studies, 2 cross-sectional studies, and 1 qualitative survey), and 24 were case reports (Figure 1).

3.2. Trials. Thirteen trials were included, reporting adverse events in 53/496 patients (10.7%) [18–30]. Three of them were randomized controlled trials (RCTs), 4 were controlled clinical trials, and 6 were single-case experimental design (SCED) trials. Six of the trials were classified as safety trials, meaning that their stated primary aim was to assess safety of interventions [18–23], whereas 7 were nonsafety trials which evaluated efficacy of interventions but also reported adverse events [24–30] (Table 2).

The safety trials [18–23] included 1 RCT, 1 controlled clinical trial, and 4 SCED trials. The only safety RCT was a double-blinded trial in 12 healthy subjects, ages 28–57, of whom 9 consumed daily doses of broccoli sprout extract combined with myrosinase (an enzyme found in all Brassica which converts glucosinolates to active isothiocyanates) over a period of 7 days. Extracts contained 25 μmol glucosinolate, 100 μmol glucosinolate, or 25 μmol isothiocyanate. No adverse events were reported [18].

The second safety trial was a double-blind controlled clinical trial in 76 subjects, ages 3–39. Thirty-eight subjects had a reported mustard allergy, and 38 age- and gender-matched controls suffered from dust-mite allergy but had no mustard allergy. Both groups underwent food challenges with mustard and a variety of other allergens. Of the 38 patients, 14 had a positive mustard challenge, of which 12 had oral allergy syndrome (pruritus, mild angioedema of lips, tongue, and throat), 1 had more severe angioedema with bronchial asthma, and 1 had systemic anaphylaxis. It is important to mention that of the 38 patients, 35 were atopic (including rhinitis, and/or bronchial asthma, atopic dermatitis) [19].

The last four safety trials were all single-case experimental design trials (SCED). The first was a trial in 10 healthy subjects, ages 21–30, which strived to determine the effect of cruciferous vegetables on phenacetin and antipyrine metabolism. Subjects started by consuming a control diet for 13 days, after which they were placed on a diet containing 300 g/day of Brussels sprouts and 200 g/day of cabbage over a period of 7 days, and finally returned to the control diet for the last 10 days. In parallel, every morning the subjects were given either 900 mg of phenacetin or 1.8 mg/kg of antipyrine. The mean plasma concentrations of either drug were measured at different intervals after administration. Researchers found that the cruciferous diet enhanced the phenacetin metabolism in the gastrointestinal tract and/or during its first pass in the liver, increasing its rate of elimination. No changes in antipyrine metabolism were noted [20]. It is worth noting that the US Food and Drug Administration ordered the withdrawal of drugs containing phenacetin in November 1983, owing to its carcinogenic and kidney-damaging properties (Federal Register of October 5, 1983 (48 FR 45466)).

The second SCED trial included 10 healthy subjects, ages 23–35, and aimed to determine the effect of cruciferous vegetables on acetaminophen and oxazepam metabolism. Subjects started by consuming a control diet for 10 days, after which they were put on a diet containing 300 g/day of Brussels sprouts and 200 g/day of cabbage over a period of 10 days, and finally returned to the control diet for the last 10 days. In parallel, every morning the subjects were given either 45 mg of oxazepam or 1500 mg of acetaminophen. The mean plasma concentrations of either drug were measured at different intervals after administration, and a 24 h urinary recovery of conjugates was performed. Researchers found that the cruciferous diet enhanced the acetaminophen metabolism and glucuronide conjugation; however, they mention

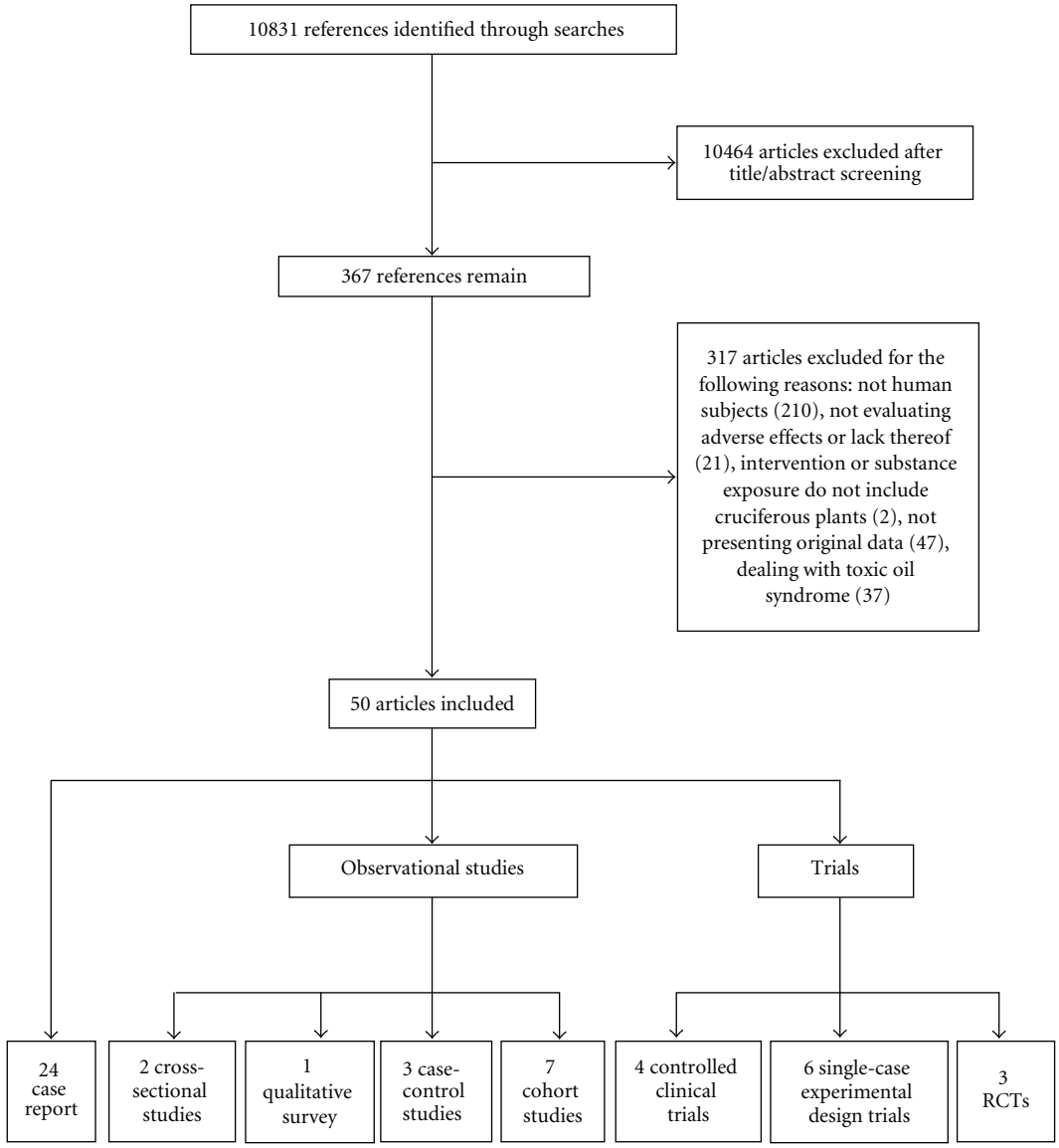

Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of study identification, inclusion, and exclusion.

that the decreased levels of cysteine conjugate in urine actually indicate reduced toxicity. No changes in oxazepam metabolism were noted [21].

The third safety SCED trial included 10 healthy subjects, ages 22–40; the goal of this study was to determine the effect of a diet rich in Brussels sprouts on warfarin metabolism. Subjects consumed their customary diets for 3 days and were then instructed to consume 400 g/day of Brussels sprouts for the next 18 days. Warfarin administration (20 mg) was provided twice on days 1 and 18. Mean plasma concentrations of warfarin were measured at different time periods, as well as prothrombin activity, and clearance rates were calculated. Researchers showed that the diet had resulted in accelerated warfarin metabolism and decreased anticoagulation [22].

The last safety SCED trial included 6 subjects, ages 20–38, with a history of recurrent allergic reactions to consumption of raw cabbage. This study aimed to determine the sensitivity profile of such patients to other cruciferous vegetables (cauliflower, mustard, and broccoli), as well as to cooked versus raw cabbage. Skin prick tests were performed for a variety of allergens; later, food challenges were performed with cooked cabbage, and levels of cabbage-specific IgE were measured in patients' sera. All patients were found to be atopic (5 with allergic rhinitis); all had positive skin prick tests to mugwort (*Artemisia vulgaris*) pollen and other aeroallergens (for instance, pollen of plants from the genera *Parietaria* and *Olea*), and 5 had positive skin prick tests to hazelnuts, walnuts, and peanuts. Mustard sensitivity (cross-reactivity with cabbage) was detected in all patients. Patients demonstrated no allergic reaction to cooked cabbage. All patients were found to have cabbage-specific IgE antibodies in their sera [23].

Table 2: Trials of cruciferous plants, their derivatives, or their constituents in humans.

Study details			Patient details			Intervention				Outcome		
Reference	Study design[1]	Setting	No. of patients/ comparators[2]	Age range	Concurrent conditions/ treatments	Plant/ substance	Route[3]	Duration[4]	Dose	Adverse events	Outcome[5]	Causality[6]
Safety trials Shapiro et al. 2006 [18]	RCT	Hospital	9/3	28–57 yrs	Healthy	Broccoli sprout extract	Oral	7 days	3 doses a day, 25 μmol glucosinolate 100 μmol glucosinolate, or 25 μmol isothiocyanate	No adverse events	NA	NA
Figueroa et al. 2005 [19]	CCT	Hospital	38/38	3–39 yrs	Reported mustard allergy. Atopy and allergies to a variety of other allergens	Mustard and a variety of other allergens	Oral	Acute exposure	Oral: increasing doses of mustard (80–6480 mg)	14 showed positive mustard challenge (12 had oral allergy syndrome, 1 had more severe angioedema with bronchial asthma, and 1 had anaphylaxis)	Resolved after symptomatic treatment	Possibly
Pantuck et al. 1979 [20]	SCED	Multisite hospital and homes	10	21–32 yrs	Healthy	Cabbage and Brussels sprouts	Oral	7 days	200 g/d cabbage and 300 g/d Brusselss sprouts	All showed accelerated phenacetin metabolism	Resolved after diet was discontinued	Likely
Pantuck et al. 1984 [21]	SCED	Multisite hospital and homes	10	23–35 yrs	Healthy	Cabbage and Brusselss sprouts	Oral	10 days	200 g/d cabbage and 300 g/d Brusselss sprouts	All showed accelerated acetaminophen metabolism, enhanced glucuronide conjugation	Resolved after diet was discontinued	Likely
Ovesen et al. 1988 [22]	SCED	Multi-site hospital and homes	10	22–40 yrs	Healthy	Brusselss sprouts, lightly steamed	Oral	2 weeks	400 g/d	All showed accelerated warfarin metabolism	Resolved after diet was discontinued	Likely

Table 2: Continued.

Study details			Patient details		Intervention				Outcome		
Reference	Study design[1]	Setting	No. of patients/ comparators[2]	Age range	Concurrent conditions/ treatments	Plant/ substance	Route[3]	Duration[4]	Dose	Adverse events	Outcome[5]	Causality[6]
Vovolis et al. 2009 [23]	SCED	Hospital	6	20–38 yrs	Recurrent allergic reactions after consuming cabbage. Atopy	Cabbage (raw versus cooked) and a variety of other allergens	Oral and topical allergy tests	Acute exposure	NA	All showed positive skin prick tests and IgE tests to raw cabbage; positive skin prick tests to a variety of allergens	NA	Possibly
Nonsafety trials Rosen et al. 1998 [24]	CCT	Hospital	18	2.5–61 yrs	Recurrent respiratory papillomatosis	Indole-3-carbinol supplement	Oral	9–24 months	200 mg twice a day for adults; for kids based on weight	Imbalance and tremor in one adult who was given twice the original dose by the researchers and unsteadiness with nausea in two pediatric patient at who by mistake took higher doses	Full resolution: in adult after returning to original dose. In pediatric cases spontaneously	Possibly
Kensler et al. 2005 [25]	RCT	Community	100/100	25–65 yrs	Healthy	Broccoli sprout infusion	Oral	12 days	Not specified	No adverse events	NA	NA
Singh et al. 1997 [26]	RCT	Multisite hospital and homes	120/118	Mean: 48 yrs	Acute myocardial infarction	Mustard oil	Oral	1 year	20 g/d	No adverse events	NA	NA
Jood et al. 2001 [27]	CCT	Community	33/33	10–12 yrs	Nutritional deficits: low serum hemoglobin and retinol	Cauliflower leaves powder, in biscuits, or shakarpara	Oral	4 months	Not specified	No adverse events	NA	NA
Rosen and Bryson 2004 [28]	CCT	Multi-site hospital and homes	33	5–71 yrs	Recurrent respiratory papillomatosis	Indole-3-carbinol supplement	Oral	10–86 months	200 mg twice a day for adults; pediatric dosage was determined by weight	No adverse events	NA	NA

Table 2: Continued.

Reference	Study details		Patient details			Intervention				Outcome		
	Study design[1]	Setting	No. of patients/ comparators[2]	Age range	Concurrent conditions/ treatments	Plant/ substance	Route[3]	Duration[4]	Dose	Adverse events	Outcome[5]	Causality[6]
Riedl et al. 2009 [29]	CCT	Single site	59/5	>18 yrs	Healthy	Broccoli sprout homogenate	Oral	3 days (once per day)	25–200 g broccoli per ingestion	No adverse events	NA	NA
Dinkova-Kostova et al. 2007 [30]	SCED	Single site	17	25–51 yrs	Healthy	Broccoli sprouts extract with daikon myrosinase, dissolved in 80% acetone and 20% water	Topical	Applied twice	Up to 40 nmol	No adverse events	NA	NA

[1] RCT, randomized controlled trial; CCT, controlled clinical trial; SCED, single-case experimental design trials.
[2] Comparator numbers appear only for controlled trials.
[3] Route of exposure.
[4] Duration of exposure.
[5] Degree of resolution in cases were adverse events were reported; NA, not applicable.
[6] The degree of association between the intervention and the adverse event, as rated by reviewers; NA, not applicable.

The nonsafety trials [24–30] included 2 RCTs, 4 controlled clinical trials, and 1 single-case experimental design trial, of which only one identified adverse events.

The trial which reported the adverse events was a controlled clinical trial in 18 subjects, ages 2.5–61, who suffered from recurrent respiratory papillomatosis and underwent complete surgical removal. All subjects received oral indole-3-carbinol supplementation for a period of 9–24 months in order to examine whether the supplements reduced the occurrence of the papillomas. Doses were 200 mg twice a day for adults, and individually calculated for pediatric patients based on body weight. Adverse events were reported in 3 patients: 1 adult, who was receiving a higher dose (400 mg twice a day) for 10 days according to the researchers' recommendation, suffered from imbalance and tremor and 2 girls, 2.5 and 12 years old, who took an overdose by mistake, suffered from unsteadiness and nausea. The symptoms in the adult resolved after returning to original dose and resolved spontaneously in the girls within a few hours to a day. According to the authors, the supplement did not cause any other side effects or complications (including acceleration of the disease) and was generally well tolerated [24]. It is unclear from this paper which other medications these specific individuals were taking, and whether they had any other acute health conditions which may have contributed to the adverse events described.

All other non-safety trials reported no adverse events with oral consumption of broccoli sprout infusion/homogenate, mustard oil, cauliflower leaves powder or indole-3-carbinol supplements, or with topical application of broccoli sprouts extract [25–30]. These studies included both adult and pediatric populations, whose concurrent medical conditions included none (healthy), nutritional deficits (haemoglobin and retinol), recurrent respiratory papillomatosis, and acute myocardial infarction (Table 2).

3.3. Observational Studies. Thirteen observational studies were included, reporting adverse events related to cruciferous plants in 1,247 patients [31–43]. Seven of them were cohort studies, 3 were case-control studies, 2 were cross-sectional studies, and 1 was a qualitative survey (Table 3).

Three cohort studies, one case-control study, and one cross-sectional survey examined prevalence of allergic reactions to oilseed rape [31–35]. In the first cohort, 7/1478 subjects who were naturally exposed to oilseed rape had either a positive skin test, a positive radio-allergosorbent test, or nasal sensitivity in response to oilseed rape exposure, whereas the proportion of such allergic reactions was 14/37 in those who were occupationally exposed to oilseed rape [31].

In the second cohort, only 147/4468 subjects with suspected oilseed allergy showed positive skin prick test to oilseed rape; most of the subjects in this study were allergic to a variety of other antigens [32].

In the third cohort, 12/22 village residents reported increased allergic symptoms during a year when oilseed rape surrounded the village, compared with a year when another crop surrounded the village. However, authors mention that the symptoms reported did not correlate with oilseed rape pollen levels measured. They were therefore not sure what the true cause could be [33].

In a case-control study, 37 people complained of seasonal allergic symptoms and bronchial reactivity in response to an unknown allergen, of whom 23 were tested. However, only 2 were found to be allergic to oilseed rape and only 10 (including those 2) were found to be atopic. The authors concluded that the symptoms could not be attributed to oilseed rape in most of these cases of seasonal allergy [34].

In the cross-sectional survey, 683/869 of village residents who were exposed to oilseed rape complained of seasonal cough, wheeze, and headaches. However, the authors concluded that the proportion of people who suffered from such symptoms was not much higher in subjects living in close proximity to oilseed rape in comparison to control subjects who do not; this suggests that the seasonal symptoms in rural areas cannot be attributed to oilseed rape allergy alone [35].

Yet another observational study dealing with allergic reactions was a cohort in 259 individuals with suspected contact allergy to foods containing allyl-isothiocyanate. Of 259 subjects who underwent allergy skin tests, 43 had a questionable reaction, of whom 15 had irritation and 3 had follicular reaction. Only two showed a true positive reaction, but one was lost to followup [36].

Three studies suggested a possible connection between cruciferous vegetables and cancer. The first was a cohort study in 64,327 women in Japan, ages 40–79, which examined the possible connection between dietary habits and risk of ovarian cancer death, based on food-frequency questionnaires. Whereas no adverse events were reported with consumption of cabbage or green leafy vegetables, a positive association was established between moderate-high consumption of Chinese cabbage and ovarian cancer. The authors suggest that this might be attributed to the fact, that, in many cases, Chinese cabbage is eaten pickled, as pickled food was proven to increase the risk of cancer [37]. The researchers did not adjust for total energy consumption, or for comalignancies such as breast/endometrial cancer; the first is important as several studies found an association between total energy consumption and increased risk for various types of cancer [38, 39]. The latter is crucial, as many women with a history of such comalignancies are at a higher risk of developing ovarian cancer than the general population [40, 41].

The second suggested a connection between cruciferous vegetables and cancer in a case-control study from Kuwait in which 313 thyroid cancer patients were paired with age- and gender-matched controls; the study's aim was to examine the relationship between different sociodemographic, medical or dietary factors and thyroid cancer, based on questionnaires. Whereas no adverse events were associated with broccoli consumption, a nonstatistically significant positive association was established between moderate-high consumption of cauliflower or cabbage and thyroid cancer ($P = 0.08$ and $P = 0.16$, resp.). The authors conclude that no clear association between consumption of cruciferous vegetables and thyroid cancer could be established [42].

The last study bringing up a possible association between cruciferous vegetable consumption and cancer is a case-control study which paired 246 thyroid cancer patients from

Table 3: Observational studies of adverse events associated with human exposure to cruciferous plants, their derivatives or their constituents.

	Study details			Patient details		Intervention				Outcome		
Reference	Study design[1]	Setting	No. of patients/ comparators[2]	Age range	Concurrent conditions/ treatments	Plant/ substance	Route[3]	Duration[4]	Dose[5]	Adverse events[6]	Outcome[7]	Causality[8]
Fell et al. 1992 [31]	Cohort	Multi-site	1515 (1478: natural exposure, 37: occupational exposure)	Adults	Atopy in some subjects	Oilseed rape	Respiratory and topical allergy tests	Acute to chronic	NA	In naturally exposed, 4/1478 showed positive skin test and 3/1478 showed positive RAST and nasal sensitivity. In occupationally exposed, 9/37 showed positive skin test and 5/37 showed positive RAST and nasal sensitivity	Not specified	Possibly
Hemmer et al. 1997 [32]	Cohort	Single site	4468	Not given	Suspected inhalant allergy to oilseed rape. Multiple allergies to other pollen allergens	Oilseed rape	Respiratory	1 year	NA	147 showed positive skin prick test to oilseed rape	NA	Possibly
Parrat et al. 1995 [33]	Cohort	Community	22	Adults	Not given	Oilseed rape	Respiratory	Seasonal	NA	Allergy (sneezing, coughing, eye irritation) in 10	Improvement when not exposed	Possibly
Lerbaek et al. 2004 [36]	Cohort	Hospital	259	Not given	Suspected contact allergy to foods containing allyl isothiocyanate	Allyl isothiocyanate 0.1% in petrolatum	Topical allergy test	Acute	NA	In 43patients: ?+ reaction, of whom 15 had irritation and 3 had follicular reaction. Two showed a true + reaction but one lost to follow up	Spontaneous resolution	Possibly

Table 3: Continued.

Reference	Study details			Patient details		Intervention				Outcome		
	Study design[1]	Setting	No. of patients/ comparators[2]	Age range	Concurrent conditions/ treatments	Plant/ substance	Route[3]	Duration[4]	Dose[5]	Adverse events[6]	Outcome[7]	Causality[8]
Sakauchi et al. 2007 [37]	Cohort	Community	64327 women	40–79 yrs	Not given	Cabbage, Chinese cabbage, green leafy vegetables, and other foods	Oral	Chronic (exact time frame given)	Varies: 0 times a week to almost every day	No adverse events with consumption of cabbage or green leafy vegetables. Of 100 women who reported moderate-high consumption of Chinese cabbage, 46 had ovarian cancer	Death	Possibly
Michnovicz and Bradlow 1997 [44]	Cohort	Community	12	22–48 yrs	No history of recent or chronic illness, drug use, or recent changes in weight	Indole-3-carbinol	Oral	7 days	5–7 mg/kg/day	No adverse events	NA	NA
Michaud et al. 2002 [45]	Cohort	Community	27111	50–69 yrs	Male smokers with no history of cancer, not using vitamins A, E or beta-carotene in excess	Cruciferous vegetables	Oral	chronic (reported intake in last 12 months)	NA	No adverse events	NA	NA
Soutar et al. 1995 [34]	CCS	Hospital	37/24	17–54 yrs	Seasonal allergic symptoms and bronchial reactivity	Oilseed rape	Respiratory	Seasonal	NA	Of the 23 cases tested, only 2 were found to be truly allergic to oilseed rape, and only 10 (including these 2) were atopic	Not mentioned	Possibly (for 2 who are allergic) Unlikely (for the rest)

Table 3: Continued.

Reference	Study details			Patient details		Intervention				Outcome		
	Study design[1]	Setting	No. of patients/ comparators[2]	Age range	Concurrent conditions/ treatments	Plant/ substance	Route[3]	Duration[4]	Dose[5]	Adverse events[6]	Outcome[7]	Causality[8]
Memon et al. 2002 [42]	CCS	Kuwait cancer control center	313/313	5–70 yrs	Cases: thyroid cancer. Either cases or controls: asthma, diabetes mellitus, gall bladder disease, hyper-tension, lupous, polyposis coli, skin allergy, skin disease (not specified)	Cabbage, cauliflower, broccoli	Oral	Chronic (exact time frame given)	Varies: 0 to 7 days a week	No adverse events with consumption of broccoli. 63/101 people with high cabbage consumption and 55/91 people with high cauliflower consumption had thyroid cancer; however, *P* trends were not statistically significant (0.08 and 0.16, resp.)	Not mentioned	Possibly
Galanti et al. 1997 [43]	CCS	Community	246/440	18–75 yrs	Not given	White and red cabbages, cauliflower, broccoli, Brusselss sprouts	Oral	Chronic (exact time frame given)	Varies: <2 to >6 times a week	56/110 people who at anytime lived in areas in Sweden where goiter and iodine deficiency were endemic until the 1960's and who reported moderate-high consumption of cruciferous vegetables had thyroid cancer	Not mentioned	Possibly
Soutar et al. 1994 [35]	CSS	Community	869/867	14–50 yrs	Both villages: 448 smokers, 325 ex-smokers	Oilseed rape	Respiratory	Chronic: months	NA	683 of 869 who were exposed had seasonal cough, wheeze, and headaches	Not mentioned	Possibly

Table 3: Continued.

Reference	Study details			Patient details		Intervention				Outcome		
	Study design[1]	Setting	No. of patients/ comparators[2]	Age range	Concurrent conditions/ treatments	Plant/ substance	Route[3]	Duration[4]	Dose[5]	Adverse events[6]	Outcome[7]	Causality[8]
Sato et al. 2004 [46]	CSS	Community	438	39–60 yrs	No history of gastric cancer or gastric ulcer	Broccoli	Oral	Chronic (exact time frame given)	Varies: never to few times a week	46/186 people who consumed broccoli once or more a week had changes in enzymes which might indicate chronic atrophic gastritis	Ongoing	Possibly
Lust et al. 1996 [47]	QS	Community	273	<4 mo	Not given	Various foods, including cruciferous vegetables (specifically cabbage, cauliflower, broccoli)	Oral (through breast milk)	Unclear (mothers were asked whether they ate different items the previous week)	Not given	63/273 exhibited colic symptoms (abdominal pain, irritability, intense crying)	Not mentioned	Possibly

[1] CCS, case-control study; CSS, cross-sectional study; QS, qualitative survey.
[2] Comparator numbers appear only for case-control and cross-sectional surveys.
[3] Route of exposure.
[4] Duration of exposure.
[5] NA, not applicable, in cases where dose cannot be quantified.
[6] RAST, radioallergosorbent test.
[7] Degree of resolution in cases were adverse events were reported; NA, not applicable.
[8] The degree of association between the intervention and the adverse event, as rated by reviewers; NA, not applicable.

Sweden and Norway with 440 age- and gender-matched controls. The goal of the study was to evaluate the relationship between certain dietary habits and the risk of follicular and papillary thyroid carcinomas. With regard to cruciferous vegetables, researchers found that for people who, at any time, resided in areas of Sweden where goiter and iodine deficiency were endemic until the 1960's, there was an increased risk for thyroid cancer with consumption of cruciferous vegetables. These findings were not reproduced anywhere else in Sweden or Norway. Authors suggest that this dual effect might be related to interactions between cruciferous vegetables and other food components such as iodine [43]. They also expressed surprise, as their findings stood in contradiction to those of many research groups that found a protective effect of cruciferous vegetables against thyroid cancer [48–51].

The next observational study included in our paper was a cross-sectional study which aimed to determine the association between broccoli consumption and chronic atrophic gastritis in 438 men, ages 39–60 years. The authors found that consumption of broccoli once or more weekly increased the risk for chronic atrophic gastritis, based on serological tests for pepsinogen I and II. However, the authors acknowledge some major drawbacks to their work. First, *H. Pylori* infection, which increases the risk for chronic atrophic gastritis, was not measured. Second, serologic criteria were used for diagnosis, meaning that the results were prone to measurement errors. Moreover, it is unclear whether the changes in enzyme profiles were accompanied by any clinical manifestations [46].

The last observational study reporting adverse events was a qualitative survey which examined the relationship between consumption of certain foods by breast-feeding mothers, and the appearance of colic symptoms in their babies (4 months old or younger). The survey conductors found a positive association between consumption of cruciferous vegetables (cabbage, cauliflower, and broccoli) and colic symptoms: abdominal pain, irritability, and intense crying [47]. This study exhibited several major limitations: first, all determinants of colic symptoms, as defined by the authors (intense crying, irritability, and abdominal pain) can be subjected to subjective interpretation; the diagnosis of infantile colic, as established over 50 years ago, requires a healthy baby to exhibit "periods of intense, unexplained fussing/crying lasting more than 3 hours a day, more than 3 days a week for more than 3 weeks" [52]. In the study, however, no such objective temporal requirements were defined; any presentation of the symptoms, regardless of duration, was considered to constitute colic. Furthermore, since the questionnaire was administered over the course of one week only, instead of the 3 weeks which are required for diagnosis of colic, it is doubtful whether such diagnosis can be made at all. Moreover, since food intake and colic symptoms were reported only for a week, it is hard to establish proper temporal relationships between the two.

Two cohort studies included in our paper identified no adverse events with exposure to cruciferous plants or their constituents; the first study included 12 subjects who ingested 5–7 mg/kg/day of indole-3-carbinol [44]. The second study, which followed 27,111 male smokers over a period of 12 months, attempted to discover whether intakes of fruits, vegetables, carotenoids, or vitamins A, E, or C could be associated with risk of bladder cancer in these people. The study determined that no association between bladder cancer risk and chronic consumption of cruciferous vegetables could be established [45].

3.4. Case Reports. Twenty-four case reports were included in the review, reporting adverse events in 35 individuals. The patients ranged from 17 to 70 years of age, whose concurrent medical conditions included allergies, both to cruciferous plants and to a variety of other allergens, asthma, bronchitis, atopy, cardiovascular diseases, and different skin conditions (eczema, pruritus, eryhtema, dermatitis, dryness and scaling, and blisters) (Table 4). The adverse events occurred after topical, respiratory, or oral exposure to different cruciferous plants, their constituents, or their derivatives. Twenty-one case reports reported allergic or hypersensitivity reactions in 31 individuals, including allergic contact dermatitis/contact urticaria, contact hypersensitivity, aggravation of eczema, cutaneous lesions similar to pityriasis rosea, asthma, rhinoconjunctivitis, aggravation of cough and chest pain, local swelling and itching, and anaphylaxis. The suspected agents triggering these reactions were turnip seeds, cabbage, broccoli, oilseed rape (flour or pollen), cauliflower, mustard (a variety of preparation forms), isothiocyanates in paint, and *Diplotaxis erucoides* (*Brassica erucoides*) pollen. It is important to note that 18 of the individuals (approximately 50% of total) had previous risk factors such as atopy, allergies to allergens unrelated to cruciferous plants (for instance, grasses, dust mite, nuts), different skin conditions, or asthma. Furthermore, 12 of those people had been exposed to the allergens occupationally, for chronic periods of time, presumably leading to the adverse events [53–73].

Two case reports documented warfarin resistance in 3 patients with cardiovascular diseases. The first patient had a prosthetic aortic valve and a history of myocardial infarctions with prolonged prothrombin time [74]. The second had pulmonary embolism, and the third suffered from an unspecified cardiovascular disease [75]. The adverse event in the first patient was attributed to excessive consumption of lettuce and greens (turnip, mustard greens, broccoli); the patient was a 35 years old woman who intended to lose weight by consuming only the above-mentioned foods, which led to a consumption of 6000 μg/day of vitamin K (60 times higher than the recommended consumption). After 5 weeks of dieting, she felt substernal chest pain and was referred to the hospital, where a myocardial infarction was diagnosed. She was treated with heparin and nitroglycerine. The second and third cases were attributed to chronic consumption of up to 450 g/day of broccoli; one of them required treatment with Coumadin. All three cases ended up in full resolution of adverse events and a recommendation to restrict consumption of vitamin K-rich foods [74, 75].

The last case report reported a suspected toxic irritative dermatitis (nonallergic) in an individual who applied a home-made mustard wrap in order to relieve the symptoms of bronchitis; authors believe the wrap may have contained some toxic compounds and concluded that the reaction was

Table 4: Case reports of adverse events associated with human exposure to cruciferous plants, their derivatives or their constituents.

Reference	Patient details		Intervention				Outcome				
	Age	Concurrent conditions/ treatments	Plant/ substance	Route[1]	Duration[2]	Dose[3]	Adverse events	Acute management	Outcome[4]	Causality[5]	Comments
Blaiss et al. 1987 [53]	21	In the past allergic rhinitis to numerous inhalant allergens: grasses, milds, ragweed, and dust mite. Immunotherapy to grass and dust allergens stopped a year prior to reported events	Cabbage (in coleslaw)	Oral	2 acute ingestions	Not specified	Anaphylaxis: pain and swelling in mouth and throat with difficult breathing. Swelling of lip, tongue, soft palate. No diffuse urticaria, wheezing or hypotension	Subcutaneous epinephrine, discharged on oral antihistamines and steroids	Full resolution	Certainly	Skin test also revealed allergy to mustard, cauliflower, and broccoli. Reexposure to coleslaw via oral ingestion after 2 weeks triggered same symptoms
Brito et al. 2001 [54]	29 and 37	Not given	Diplotaxis erucoides (wall rocket) pollen	Respiratory	2 months every year	NA	Patient 1: rhinoconjunctivitis Patient 2: rhinoconjunctivitis and asthma. Patients were tested and found to be allergic to *Diplotaxis erucoides* pollen		Not mentioned	Likely	Occupational exposure
Compes et al. 2007 [55]	38	Ex-smoker, with a personal history of house dust mite allergic rhinitis and asthma, and a family history of atopy	Turnip seeds	Topical and respiratory	Chronic (exact duration not mentioned)	NA	Rhinitis and asthma. Patient was tested and found to be allergic to turnip seeds	Not mentioned	Not mentioned	Possibly	Bird fancier. Patient was also found to be allergic to avian antigens

Table 4: Continued.

Reference	Patient details		Intervention				Outcome				
	Age	Concurrent conditions/ treatments	Plant/ substance	Route[1]	Duration[2]	Dose[3]	Adverse events	Acute management	Outcome[4]	Causality[5]	Comments
Caldan 1981 [56]	28	Eczema and hay fever. In the past contact with other vegetables caused itching	Cabbage	Topical	Not reported (unclear whether chronic eczema is related to cabbage exposure)	NA	Contact urticaria. Patch test revealed allergy to "green leaves" (cabbage and Brusselss sprouts)	Not mentioned	Not mentioned	Possibly	Paper lacks many details regarding both urticaria and eczema
Chakrabarti et al. 2003 [57]	56	3-year history of severe eczema and recurrent blisters on palms	Broccoli	Topical	Chronic (exact duration not mentioned)	NA	Allergic contact dermatitis (worsening of eczema)	Subcutaneous epinephrine, discharged on oral antihistamines and steroids	Partial resolution: eczema improved upon avoidance of topical contact with broccoli and other vegetables	Possibly	Patient refused patch tests to other vegetables, but it is possible that she is allergic not only to broccoli
Dannaker et al. 1987 [58]	38	2 year history of hand dermatitis; 6 months history of dryness and scaling at angles of mouth (Unclear whether her hand dermatitis is related to mustard exposure)	Mustard in salad dressings	Topical	Chronic, for the past 3 years	NA	Acute episode of allergic contact dermatitis	Not mentioned	Not mentioned	Possibly	Occupational exposure

Table 4: Continued.

Reference	Patient details		Intervention				Outcome				
	Age	Concurrent conditions/ treatments	Plant/ substance	Route[1]	Duration[2]	Dose[3]	Adverse events	Acute management	Outcome[4]	Causality[5]	Comments
Di Giacomo et al. 1998 [59]	48	Not given	Oilseed rape flour	Respiratory	Chronic (exact duration not mentioned)	NA	Episodes of asthma and rhinoconjunctivitis Allergy tests showed that skin prick tests were only mildly positive for oilseed rape flour, and the peak respiratory flow only slightly decreased during exposure	Not mentioned	Not mentioned	Possibly	Occupational exposure
Hernandez et al. 2005 [60]	70	Allergies to some fruit and nuts, seasonal allergic rhinoconjunctivitis	Cauliflower	Oral	Acute ingestion	Not specified	Oropharyngeal itching, facial and hand swelling, severe bronchospasm	Required emergency room consult	Full resolution	Possibly	No details of what other components the dish included

Table 4: Continued.

Reference	Patient details		Intervention				Outcome				
	Age	Concurrent conditions/ treatments	Plant/ substance	Route[1]	Duration[2]	Dose[3]	Adverse events	Acute management	Outcome[4]	Causality[5]	Comments
Jorro et al. 1995 [61]	43, 17, and 19	Patient 1: history of IgE-dependent rhinitis since childhood; urticaria angioedema episodes related with shellfish. Patient 2: history of IgE-dependent asthma and rhinitis and urticaria to latex. Patient 3: history of IgE-dependent rhinitis	Mustard sauce	Oral	Acute ingestions	Not specified	Patient 1: episodes of pruritus, swelling of tongue, dysphagia, dysphonia, facial edema, and progressive upper respiratory difficulty. On one occasion, he experienced hypotension, and on another urticaria and palpebral edema. Patient 2: episodes of pruritus, swelling of lips and tongue, and edema. Patient 3: dysphonia, dysphagia, progressive upper respiratory difficulty, and generalized urticaria. Upon allergy testing, patients were found to be allergic to mustard	Not mentioned	Full resolution	Likely	None
Lingelbach et al. 2003 [62]	40	For the past 11 years: episodes of exercise-induced anaphylaxis after eating, once or twice a year	Cabbage and mustard	Oral	Acute ingestions	NA	Anaphylaxis induced by exercise after ingestion of cabbage or mustard	IV adrenaline, antihistamine, and corticosteroids	Full resolution	Likely	Patient was also found to be allergic to other foods

Table 4: Continued.

Reference	Patient details		Intervention				Outcome				
	Age	Concurrent conditions/ treatments	Plant/ substance	Route[1]	Duration[2]	Dose[3]	Adverse events	Acute management	Outcome[4]	Causality[5]	Comments
Meding 1985 [63]	40	Vesicular hand eczema for the past 9 years, sometimes worsened for no clear reason, and also after every mustard ingestion	Mustard and rapeseed	Oral (however, allergy testing was topical)	Acute ingestions	Not specified	Vesicular episodes (worsening of eczema). Positive skin prick test to crushed seeds of rapeseed	Not mentioned	Partial resolution: eczema improved upon avoidance of mustard and rapeseed	Possibly	Apart from ingestion, patient was also occupationally exposed to rapeseed

Table 4: Continued.

Reference	Patient details		Intervention				Outcome				
	Age	Concurrent conditions/ treatments	Plant/ substance	Route[1]	Duration[2]	Dose[3]	Adverse events	Acute management	Outcome[4]	Causality[5]	Comments
Pasricha et al. 1985 [64]	35 and 47	Patient 1 had suffered from dermatitis ever since she was 15, which worsened when handling cattle food. Patient 2: itching and erythematous papules for the past 1.5 years, for which she was treated	Patient 1: mustard; Patient 2: mustard khal	Topical	Chronic (exact duration not mentioned)	NA	Patient 1: itching and erythmatous papular lesions on forearms, arms, neck, forehead, ear lobules, and sides of face for the past 8 months. Patient 2: itching and erythmatous papules on forearms, forehead, cheeks, ear lobules, neck, and dorsum of feet for the past 1.5 years. Upon allergy testing, patient 1 found to be allergic to mustard, jowar flour, and wheat flour. Patient 2 found to be allergic to mustard khal and maize	Not mentioned (it is mentioned that treatment was given, but no further details are provided)	Improved with treatment, but authors do not mention what happens when not exposed	Possibly (patient 1), unlikely (patient 2)	Patient 1 had been using mustard oil for years and only lately did she start experiencing adverse event. Patient 2 did not report any exposure to mustard
Quirce et al. 2005 [65]	41	Allergic rhinoconjunctivitis to pollen. For past 7 years: episodes of ocular and nasal itching, sneezing, watery nose, tearing, dry cough, chest tightness, and dyspnea after inhaling cauliflower or cabbage vapors	Cabbage	Oral	Acute ingestion	Not specified	Generalized urticaria, facial and oropharyngeal angioedema. Upon allergy testing (with cabbage or cauliflower): severe rhinoconjunctivitis and an early asthmatic reaction	Required emergency room consult	Full resolution	Possibly	Occupational exposure

Table 4: Continued.

Reference	Patient details		Intervention				Outcome				
	Age	Concurrent conditions/ treatments	Plant/ substance	Route[1]	Duration[2]	Dose[3]	Adverse events	Acute management	Outcome[4]	Causality[5]	Comments
Rosenberg and Gervais 1986 [66]	42 and 34	Patient 1: asthma triggered by isocyanate paint. Patient 2: ex-smoker, asthma triggered by isocyanate paint	Patient 1: mustard and horseradish. Patient 2: mustard, radish, turnip	Oral	Acute ingestions	Not specified	Patient 1: face flushing, asthma attack. Patient 2: asthma attack	Patient 1: not mentioned; Patient 2: hospitalized, treated w/theophylline	Full resolution. In patient 2: recurrence when eating mustard/radish	Likely	Occupational exposure. No testing done for food allergies in either patients
Sanchez-Guerrero and Escudero 1998 [67]	36 and 54	Patient 1: for past 7 years: pruritus, erythema, vesicles, fissures, and peeling in both hands, as well as facial angioedema, within 6–8 h after handling broccoli. Patient 2: asthma; in past 4 years, papules and vesicles in both hands and eyelids 24–36 hours after exposure to cauliflower or broccoli	Broccoli or cauliflower	Topical	Chronic (exact duration not mentioned)	NA	Patient 1: acute episodes of contact dermatitis after handling broccoli; Patient 2: acute episodes of contact dermatitis after handling broccoli or cauliflower	Not mentioned	Patient 1: full resolution after avoiding broccoli. Patient 2: no resolution even when avoids allergens	Possibly	Occupational exposure
Schulze and Wollina 2003 [68]	19	Not given	Mustard (sauce and oil)	Oral and topical	varies (acute to chronic)	Not specified	At 4 years of age-topical exposure caused eye lacrimation and cauterization, and dyspnea. Upon ingestion at age of 19: angioedema and bronchospasm	Topical and oral antihistamines	Not mentioned	Possibly	Some mustard allergy tests were positive but rubbing test was negative. Cross-reactivity with other Brassica

Table 4: Continued.

Reference	Patient details		Intervention				Outcome				
	Age	Concurrent conditions/ treatments	Plant/ substance	Route[1]	Duration[2]	Dose[3]	Adverse events	Acute management	Outcome[4]	Causality[5]	Comments
Suh et al. 1998 [69]	43	Smoker; cough and chest pain	Oilseed rape dust	Respiratory	Chronic	NA	Aggravation of cough and chest pain	Not mentioned	Not mentioned	Possibly	Occupational exposure; allergy testing not performed
Valero et al. 1995 [70]	34, 31, 25, 52, and 33	Patient 1: house dust allergy. Patient 2: seasonal rhinitis. Patient 3: peach allergy; seasonal rhinitis; familial atopy. Patient 4: seasonal rhinoconjuctivitis and bronchial asthma, family pollen allergy.	Mustard sauce or mustard pollen	Oral and respiratory	Acute (ingestion) to seasonal (pollen inhalation)	Not specified	Patient 1–3: urticaria, facial edema, rhinoconjunctivitis/rhinitis. Patient 4: facial edema, bronchospasm, rhinitis. Patient 5: urticaria, facial edema, and bronchospasm. All found to be allergic to mustard	Not mentioned	Full resolution	Possibly	None

Table 4: Continued.

Reference	Patient details		Intervention				Outcome				
	Age	Concurrent conditions/ treatments	Plant/ substance	Route[1]	Duration[2]	Dose[3]	Adverse events	Acute management	Outcome[4]	Causality[5]	Comments
van Ketel et al. 1975 [71]	43	Eczema in past 10 years	Cauliflower	Topical	Chronic (exact duration not mentioned)	NA	Aggravation of eczema. Upon allergy testing was found allergic to both cauliflower and other Brassica: Brusselss sprouts and red cabbage	Not mentioned	Not mentioned	Possibly	Occupational exposure. Aggravation of eczema also occurs after contact with onions, tulip bulbs, rubber gloves, and pesticides, but to a lesser extent
Widstrom and Johansson 1986 [72]	25	As a child, severe atopic dermatitis, rhinitis and swelling of throat in reaction to fish or egg. Currently, rhinitis when exposed to cats or dogs	Mustard (in mustard sauce or mayonnaise)	Oral	Acute ingestions	Not specified	Acute episodes of urticaria and angioneurotic edema of face and neck. Upon allergy testing was found to be allergic to mustard	Not mentioned	Full resolution	Possibly	None
Zawar 2005 [73]	25	Healthy	Mustard oil	Topical	Several acute applications	NA	Cutaneous lesions similar to pityriasis rosea (appeared after first application)	Corticosteroids and antihistamines	Full resolution followed by recurrence on re-exposure	Certainly	None
Walker 1984 [74]	35	Prosthetic aortic valve, history of myocardial infarctions with prolonged prothrombin time. Treated with warfarin and dipyridamole	Lettuce and greens (e.g., turnip, mustard greens, broccoli)	Oral	5 weeks	Not specified. Authors do mention, however, that vitamin K intake was 6000 μg per day	Diet-induced warfarin resistance which led to substernal chest pain and myocardial infarction	Referred to hospital, where she was treated with nitroglycerin and heparin	Full resolution	Likely	Vitamin K consumption was 60 times more than the norm (360 μg)

Table 4: Continued.

Reference	Patient details		Intervention				Outcome				
	Age	Concurrent conditions/ treatments	Plant/ substance	Route[1]	Duration[2]	Dose[3]	Adverse events	Acute management	Outcome[4]	Causality[5]	Comments
Kempin 1983 [75]	Not given	Patient 1: pulmonary embolism; Patient 2: cardiovascular disease (not specified which). Treated with heparin and Coumadin (=warfarin)	Broccoli	Oral	Chronic (exact duration not mentioned)	Up to 450 g/day	Warfarin resistance	Coumadin anticoagulation in patient 2	Full resolution	Likely	None
Geier 1991 [76]	45	Bronchitis	Home-made mustard wrap, containing ground mustard seeds and water	Topical	Acute application (20 minutes)	Not specified	Toxic irritative dermatitis	Topical corticosteroids	Full resolution	Possibly	Authors labeled case as toxic irritative dermatitis and NOT an allergic reaction and warn against use of home-made medications

[1] Route of exposure.
[2] Duration of exposure.
[3] NA, not applicable, in cases where dose cannot be quantified.
[4] Degree of resolution in cases here adverse events were reported; NA, not applicable.
[5] The degree of association between the intervention and the adverse event, as rated by reviewers; NA, not applicable.

not an allergic one. Hence, they advised against the use of home-made wraps. The patient was treated with corticosteroids with full resolution. This case was very brief and lacked a great deal of information regarding previous medical history and whether other medications had been used to treat the patient's bronchitis. Moreover, no test was conducted to verify the cause of the adverse event [76].

3.5. Excluded Papers. Of the 317 papers excluded, 280 did not fulfill the criteria for our systematic review (i.e., they did not evaluate adverse effects or lack thereof, intervention or substance exposure did not include cruciferous plants, or did not present original data). Another 37 articles were excluded since they dealt with toxic oil syndrome. In order to promote transparency in our decision-making process, we shall explain the rationale behind excluding this latter group of papers.

Toxic oil syndrome is the name given to a disease outbreak in Spain in 1981. Its first appearance was as an acute lung disease, which was followed by a range of other chronic symptoms affecting the lungs, the liver, the kidneys, the skin, the joints, the central nervous system, and the immune system [77–83]. The cause for the disease was traced to the consumption of cheap, refined, rapeseed oil that had been intended for industrial use rather than for human consumption. It was sold as "olive oil" and was therefore used for cooking. According to the World Health Organization, toxic compounds derived during the refinement process, used to remove the aniline and to denature oils intended for industrial use, were responsible for causing the disease. Hence, toxic oil syndrome has come to be considered a chemical incident, rather than a side effect associated with consumption of rapeseed oil, since consumption of non-industrial rapeseed oil does not cause the disease. In fact, the specific refinement process of the oil that caused the disease was so unique that experimental studies performed in a variety of laboratory animals have hitherto failed to reproduce the symptoms of human toxic oil syndrome [84].

4. Discussion

Research conducted in the last decade supports the notion that some cruciferous plants and their derivatives may serve to prevent or attenuate several medical conditions. To further this field of investigation, we conducted this systematic paper to determine the safety parameters surrounding the use of cruciferous plants. In this regard, our review identified adverse events in 1335 individuals, out of a total of 101,198 individuals who were included in all studies. Of these, 1292 adverse events were ranked as only possibly or unlikely to be caused by cruciferous plants. Only 43 were determined to have been certainly or likely caused by exposure to cruciferous plants. Adverse events, which could certainly or likely be attributed to members of the *Brassica* genus, included allergic reactions (including anaphylaxis), changes in metabolism of acetaminophen, phenacetin and warfarin, and warfarin resistance. Most adverse events reported in our paper were allergic or hypersensitivity reactions; however, their significance for the general healthy population is hard to infer, due to confounding medical histories or low causality ratings. Adverse events from both allergy trials and case reports were mostly in individuals who suffered from atopy, allergies to cruciferous plants and/or other allergens (for instance, grasses, ragweed, dust mite, pollen, dogs, cats and different fruit and nuts), asthma, or a variety of skin conditions such as eczema, pruritus, erythema, dermatitis, dryness and scaling, or blisters. A possible conclusion from these case reports, however, is that occupational exposure to Brassica plants may predispose to develop an allergy to these plants. With regards to observational studies which investigated allergies to cruciferous plants or their derivatives, all concluded that the cases could not be attributed to the suspected culprits.

A second category of adverse events included changes in metabolism of phenacetin, acetaminophen, and warfarin. While phenacetin has been banned for use by the FDA, acetaminophen and warfarin continue to be widely used. As such, it was important to understand if these changes in metabolism pose any risk to those who use these drugs. As for acetaminophen, the authors explain that the decreased levels of the cysteine conjugate of acetaminophen found in subjects' urine actually indicate decreased toxicity; thus, cruciferous plants may not pose any risk to individuals who consume acetaminophen. With regards to warfarin, however, the finding that cruciferous vegetables alter its metabolism might bear greater clinical relevance. It has been suggested that foods high in vitamin K, such as cruciferous vegetables, may interact with warfarin and its anticoagulant activity. In all case reports describing warfarin resistance, the patients had consumed very large amounts of cruciferous vegetables (up to 450 g/day or the equivalent of 6000 μg vitamin K/day), amounts not warranted for consumption by the general population. However, it is possible that lower doses would have some effects on anticoagulation as well. Similarly large amounts of cruciferous vegetables (400 g/day) were given to subjects in the SCED trial which examined changes in warfarin resistance. As many foods interact with warfarin, among which are mango, avocado, fish oil, soy milk, and foods high in vitamin K [84], it is imperative for physicians to discuss the consumption of such foods (including cruciferous vegetables) with their patients when starting treatment with anticoagulants.

Reports of other types of adverse events identified in our systematic review, including cancer, chronic atrophic gastritis, infantile colic, and toxicity-related events, could only be ranked as possibly or unlikely to be caused by exposure to cruciferous plants, as there was not enough evidence to establish a stronger causal relationship between the suspected culprits and the adverse events. Further research employing better methodology should be undertaken in order to establish whether positive association exists between consumption of Brassica vegetables and any of the above-mentioned adverse events.

Finally, a number of studies did not find any adverse events associated with consumption of cruciferous plants or their derivatives in subjects with a variety of health conditions, including history of myocardial infarction, nutritional deficits, or recurrent respiratory papillomatosis, or in healthy individuals.

In summary, to date, adverse events presumably related to cruciferous plants have been reported in 1335 individuals, identified through 50 studies which included a total of 101,198 individuals. However, the number of those which were certainly/likely caused by Brassica plants (including allergic reactions, changes in drug metabolism, and warfarin resistance) was much lower: only 43 of all reported adverse events received such high causality rating. For comparison, the literature shows that the pooled prevalence of adverse drug reactions ranges from 4.2 to 6% [85]. This frequency, if applied to cruciferous plants, would translate into 4250–6072 reports of adverse events out of the included 101,198 individuals, a value much higher than what was found in our current study.

When analysing our findings, one must bear in mind that the total number of individuals included in all studies comprises both those who were definitely exposed to Brassica plants and those who were presumptively exposed as the degree of exposure could not be ascertained in all cases. This might cause the frequency of occurrence of adverse events to appear lower than the actual value. On the other hand, our study also included case reports of individuals, all of whom were exposed, and reported adverse events. In this regard, the frequency of adverse events tends to be an overestimation, since individuals who are exposed, but do not experience an adverse event, are likely not to report. Hence, the inclusion of these case report, in which essentially all individuals exposed report adverse events, may serve to balance this underestimation. We advise the reader to treat the broad pooled frequency presented in the previous paragraph (1335/101,198) as merely gross estimations of the actual frequency, as conducting a meta-analysis *per se* was deemed inappropriate given the heterogeneity of study parameters (subjects, interventions, clinical outcomes, and study designs).

We conclude that cruciferous plants are generally safe for human consumption and use. However, individuals with known allergies/hypersensitivities to a certain member of the *Brassica* genus, or those taking warfarin, should consult with their physician before consuming such vegetables. In the future, if cruciferous derivatives are to be investigated as potential therapeutic agents, we recommend that adverse events be monitored. As our findings reflect positively on the safety of Brassica plants in humans and evidence from the current experimental literature of their benefit in certain disease states, we would encourage further exploration of their potential use in the clinical setting. The use of *brassica* or similar food products may have the potential to provide a safer alternative for the treatment of disease in comparison to current pharmaceutical interventions.

Conflict of Interests

The authors declare no conflict of interests.

Author Contribution

JYY initiated the research question; OS, EGC, DA, SS, SV, and JYY designed research; OS, EGC, DA, and SS conducted research; DA and SS provided essential materials; OS and EGC, analyzed data; OS wrote the paper; OS, EGC and JYY had primary responsibility for final content. SV provided guidance on study design and interpretation, including paper revisions. All authors read and approved the final paper.

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