J Food Sci Technol (June 2015) 52(6):3169–3186
DOI 10.1007/s13197-014-1558-5

REVIEW

Role of antioxidants and phytochemicals on acrylamide mitigation from food and reducing its toxicity

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Revised: 25 August 2014 / Accepted: 8 September 2014 / Published online: 18 September 2014

Abstract Nowadays, the presence of acrylamide in lots of fried and baked foods raises concerns due to its potential to cause toxicity and cancer in animals and human. Consequently, a number of papers have focused on evaluation of various chemicals in reduction of acrylamide in various food sources, as well as decreasing its related toxicities. In addition, plants are important sources of diverse metabolites demonstrating either possible effectiveness in acrylamide toxicity or reduction of acrylamide content in food sources. In this paper, we have criticized all relevant studies in terms of acrylamide mitigation from food by phytochemicals and antioxidants, and the influence of herbal medicines and phytopharmaceuticals on reduction of acrylamide toxicity in both animals and human.

Keywords Acrylamide · Antioxidants · Baked foods · Fried foods · Phytoceuticals

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Introduction

The chemical formula C_3H_5NO represents a well-known compound named "acrylamide" (acrylic amide; prop-2-enamide), which is a white odorless water soluble crystal, although it can be solved in other chemical solvents like ethanol, ether, and chloroform. Generally, acidic and basic materials, as well as oxidizing agents together with iron and iron salts, are able to destroy this structure to generate ammonia. However, it can also be decomposed by high temperature to form both carbon monoxide and dioxide, and nitrogen oxides (Sigma-Aldrich 2014).

Today, acrylamide is industrially prepared by the hydrolysis of acrylonitrile using nitrile hydratase. This compound is mainly applied in polyacrylamides production usually employed as a water-soluble thickener. Polyacrylamide is able to produce a water soluble gel, which is very useful in electrophoresis and famous as SDS-PAGE (Sodium dodecyl sulfate polyacrylamide gel electrophoresis). There are some other applications for this polymer such as papermaking, tertiary oil recovery, and the manufacturing of permanent press fabrics. The monomeric acrylamide can be used industrially to provide dyes and other monomers (Office of Pollution Prevention and Toxics. Chemical Summary for Acrylamide. United States Environmental Protection Agency. EPA 749-F-94-005a. Last access: Feb12 (2014).

In 2002, some reports revealed that acrylamide could be found in lots of fried and baked foods. Consequently, recent articles are concerned with whether acrylamide can cause considerable toxicity and cancer in both animals and human or not (Simonne et al. 2014) In this review, we aimed to give an overview on the present background information of acrylamide, its natural contents in food sources, and toxicity in both animals and human, as well as the role of phytopharmaceuticalsand antioxidants on mitigation of acrylamide from foods and reduction of its toxicities.

Formation of acrylamide in foods during cooking process

These days, cooking is a respected art form. However, there have been some concerns with the creation of acrylamide during the cooking process. In fact, acrylamide is not found naturally in its sources but can be formed when sugars and amino acids react with each other in carbohydrate (and/or protein)-rich foods during the cooking process due to high temperatures. Actually, this monomeric compound can be found in a number of foods such as potato chips, fries, breads, cereals, even coffee during high temperature cooking including toasting, frying and baking. The darker the color of the fried or baked food (e.g., French fries or toast), the higher the presence of acrylamide (Acrylamide: a natural process in cooking June (2010).

Tareke et al. (2002)) reported the moderate concentration of acrylamide (5–50 ppb) in heated protein-rich foods, while a higher content (150–4000 ppb) in carbohydrate-rich foods (potato, beetroot and selected commercial potato products) for the first time. They also reported different concentrations of acrylamide (1,200, 450 and 410 ppb) in potato chips, biscuits, as well as French fries and crackers, respectively. Moreover, the above mentioned researchers concluded that acrylamide did not exist in the same foods when used as raw materials or boiling water cooked (Tareke et al. 2002). Most references report mean or average acrylamide level in particular periods but some factors like sampling date and distribution of acrylamide content over evaluation period are so effective on quantification process and must be considered carefully (Wenzl and Aklam 2007). Another important problem, dietary intake of acrylamide in different populations, has been evaluated in different previous researches (Claeys et al. 2010; ANSES, 2011; FDA/CFSAN, 2006; OEHHA-CAL/EPA, 2005). Acrylamide level in different food groups on the basis of various reliable references are summarized in Table 1. An appraisal on Table 1 shows that although the measured amounts of acrylamide have been reported in a wide range, French Fries, potato chips, biscuits, roasted coffee and green teas as well as decaffeinated ones, and also different types of breads could be the main sources of oral exposure to this compound.

Role of antioxidants in acrylamide content mitigation in foods

The correlation between antioxidant phytochemicals and acrylamide can be considered from two points of view. The first one describes antioxidants as exogenous additives, while the second one views them as endogenous secondary metabolites.

1 Using additives like organic acids, amino acids and mono- and divalent cations, as a mitigating strategy to control acrylamide content in foods, has been fully discussed in "CIAA toolbox for acrylamide" and different previous review studies (Capuano and Fogliano 2011; CIAA 2011; Friedman and Levin 2008; Capuano and Fogliano 2011; Zhang and Zhang 2007a; Zhang et al. 2009b).

Lack of sufficient studies and discordance in available results, impede logical judgment about the effectiveness of antioxidants. This is especially true regarding phenolic compounds such as flavonoids, phenolic acids, and tannins, as exogenous controllers on food acrylamide level. In some cases, it seems that antioxidant activity is not mainly responsible for changing the acrylamide content. This conflicting situation may be attributed to the chemical diversity of antioxidants. In fact, according to the unique structure of each antioxidant, it can play a specific role in either the promotion or reduction of acrylamide formation, sometimes regardless of its antioxidant potency.

Despite some reports about the beneficial effect of curcumin as a potent antioxidant to reduce acrylamide formation, a recent study showed that it can facilitate acrylamide production. This is due to the carbonyl moieties, which react with aspargine to finally produce acrylamide. On the other hand, naringenin, with weak antioxidant activity, can strongly react with the amide group of intermediates in the Maillard reaction and block acrylamide formation (Jin et al. 2013; Hamzalioglu et al. 2013; Zhang and Zhang 2007a). Moreover, there are some other parameters influencing acrylamide production including reaction condition, solubility, concentration, and preparation method for antioxidants, which can confusingly cause opposite results for the same kind of agent (Jin et al. 2013).

2 A limited studies supposed a negative correlation between acrylamide formation and phenolic (anti-oxidative) composition of its raw natural source (Evers and Deuber 2012). Moreover, Zhu et al. (2010) revealed that hydroxycinnamoylquinic/hydroxycinnamoyl derivatives are the major phenolic compounds in potatoes. They also showed that total phenolic content was reversely correlated with aspargine (−0.590) and total sugar quantity (−0.488) in raw potato and acrylamide content (−0.691) in processed form. Kalita et al. (2013) concluded that acrylamide content in fried potato has a negative relation to total phenolic (−0.367) and chlorogenic acid content (−0.359) of raw material. However, the presence of excess sugar can block this beneficial effect.

A few studies have focused on groups of phytochemicals other than phenolics like sulfur or nitrogen containing natural products. The acrylamide reducing activity of garlic is attributed to sulfur groups of alliin and allicin, or their free radical scavenging activity (Casado et al. 2010; Jin et al. 2013; Yuan et al. 2011). Moreover, a nitrogenous compound, piperin, weakly reduces acrylamide content in the aspargine/glucose model system (Zhu et al. 2009).

Table 1 Acrylamide level in selected food groups based on different reliable references

Food	Acrylamide concentration (ppb=μg/kg)									
	1	2, a	3, b	4, c	5, b	6, b	7	8, d	9, c	10, d
Cereals and cereal based products			343	70 (5–1649)					189 (‹30–1346)	
Breakfast cereals	119.4	138 (132–144)	96		86	16.2	‹10–1649	139 (35–325)		84 (5–545)
Bread		30 (25–35)	446	50 (5–1987)	31	34.3	‹10–3200	16 (3–51)	30 (12–162)	
Ginger bread		415 (414–415)		303 (5–7834)						501 (5–6141)
Popcorn				145 (5–3100)	180			328 (205–451)	416	
Biscuits			350	145 (4–3324)	37	139	18–3324	380 (27–1573)	100 (22.5–1035)	
Pizza			33		20	41				
Root and tubers			477							
Potato chips	597.5		334	186 (5–4653)	466	724.1	117–4215		1115 (‹60–3100)	268 (5–2310)
French fries		338 (336–339)			413		59–5200	239 (41–1285)	320 (‹60–12000)	
Restaurants	404.1									
Oven bake	697.8									
Potato crisps		675 (674–676)	752	528 (5–4215)		954.5		835 (220–2061)		652 (5–4215)
Croquettes			110							
Stimulants and analogue			509							
Coffee									255 (200–310)	
Not brewed			288			68				
Brewed	7.8		13		7					
Roasted		256 (255–257)	288	320 (79–1188)			45–935	212 (172–243)		310 (101–935)
Instant		1123						865 (724–997)		
Decaffeinate			668							
Cocoa products			220			80	‹2–826	442 (176–707)		
Green tea (roasted)			306							
Vegetables			17							
Raw			4.2							
Processed			59							
Fruits										
Fresh			‹1			2				
Processed			131							
Canned olive	242.8				414			884		
Nuts and oilseeds			84							
Almond (roasted)					320					
Peanut (roasted)					27					
Peanut butter					88					

Table 1 (continued)

Food	Acrylamide concentration (ppb=μg/kg)									
	1	2, a	3, b	4, c	5, b	6, b	7	8, d	9, c	10, d
Sunflower					39.5					
Condiments and sauces			71							
Infant formula			˂5				˂10–130			
Baby foods		69 (64–74)		67 (5–432)				13 (3–27)		
Canned, jarred			22							
Dry powder			16							
Biscuits		86 (83–90)	181	79 (5–910)						106 (5–432)
Cereal based		51 (45–57)						65 (3–598)		
Alcoholic beverages			6.6							

[1] Food and Drug Administration, Center for Food Safety and Applied Nutrition, FDA/CFSAN, 2006

[2] European Food Safety Authority, EFSA Journal 2012,10:2938

[3] Summary and conclusions of the sixty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives, JECFA. Rome, 2005

[4] European Union database on acrylamide levels in food- update and critical review of data collection, Food Additives and Contaminants, 2007, 24(S1): 5–12

[5] Office of Environmental Health Hazard Assessment/California Environmental Protection Agency, OEHHA-CAL/EPA., 2005

[6] French agency for food, environmental and occupational health and safety, ANSES, Second French Total Diet Study (TDS 2), Pesticide residues, additives, acrylamide and polycyclic aromatic hydrocarbons, 2011

[7] Lineback, et al. 2012

[8] Food Standard Agency UK, A rolling programme of surveys on process contaminants in UK retail foods, Acrylamide and Furan: Survey 4, 2012

[9] Joint Institute for Food Safety and Applied Nutrition and National Center for Food Safety and Toxicology, JIFSAN/NCSF, 2002

[10] Gobel and Kliemant 2007

[a] Values indicate middle bound and ranges in brackets indicate lower bound and upper bound values in 2010

[b] Mean concentration

[c] Values indicate median and ranges in brackets indicate minimum and maximum values

[d] values indicate mean and ranges in brackets indicate minimum and maximum values

Table 2 Effect of natural compounds on acrylamide content mitigation

Phytochemical name	Used system	Acrylamide reduction (%)	Other parameters	References
Rutin (1 mmol/ml, 100 μl)	Model (aspargine/glucose)	49.4	180 °C for 15 min	Zhu et al. 2009
P-coumaric acid		53.4		
Gallic acid		47.7		
Quercetin		38.4		
Chlorogenic acid		25.5		
(+)-Catechin		23.5		
Hesperedin		16.7		
Naringenin		13.9		
Piperine		13		
Ferulic acid		-		
Hesperetin		-		
Caffeic acid	Model (aspargine/glucose)	-	180–200 °C for 7 min	Bassama et al. 2010
Catechin		-		
Cinnamic acid		-		
Ferulic acid		Slight promotion		
Coumaric acid		-		
Gallic acid		-		
Epicatechin		-		
Tyrosol	Model (aspargine/glucose)	Up to 50	180 °C for 20 min	Kotsiou et al. 2010
Oleuropein		-		
Gallic acid		-		
Ferulic acid	Model (aspargine/glucose)	Up to 50	105–125±2 °C for 10–60 min	Kotsiou et al. 2011
Caffeic acid		Up to 50		
Gallic acid		Up to 70		
Protocatechuic acid		Up to 70		
Curcumin (0.05–2 % *w*/*w*)	Model (starch based)	Up to 47	190 °C for 20 min	Zhu et al. 2011
Proanthocyanidins		Up to 62		
Eugenol (0.25–4 % *w*/*w*)	Food (cooky)	Up to 42	210 °C for 15 min	
Cinnamaldehyde		Up to 34		
Curcumin		Up to 40		
Allicin (0.0375 %)	Model (asparagine/sugar)	>50	700 Watt for 20 min	Yuan et al. 2011
Rutin (10^{-2}—10^{-9} mol/L)	Model (asparagine/sugar)	Up to 60	180 °C for 5 min	Cheng et al. 2013
Kaempferol-3-O-glucoside		Up to 40		
Quercetin		Up to 50		
Quercetin-3-O-glucoside		Up to 60		
Myricetin		Up to 66		
Kaempferol		Up to 50		
Ferulic acid	Food (potato chips)	76.71	190±5 °C for 6 min	Abdel-Monem et al. 2013
Protocatechuic acid		31.81		
Caffeic acid		73.33		
Catechin		90.90		
Gallic acid		98.03		
Phytic acid (0.1 M)	Model (β-alanine/glucose)	–	100–105 °C for 180 or 300 min	Wang et al. 2013
Caffeic acid (0.05 M)	Model (aspargine/fructose)	30	Model: 180 °C for 15 min	
Food: 185 °C for 15 min	Oral et al. 2014			
	Food (biscuit)	19		
Chlorogenic acid	Model (aspargine/fructose)	45		
	Food (biscuit)	15		
Ellagic acid	Model (aspargine/fructose)	69		
	Food (biscuit)	19		

Table 2 (continued)

Phytochemical name	Used system	Acrylamide reduction (%)	Other parameters	References
Epicatechin	Model (aspargine/fructose)	74		
	Food (biscuit)	17		
Oleuropein	Model (aspargine/fructose)	-		
	Food (biscuit)	17		
Punicalagin	Model (aspargine/fructose)	85		
	Food (biscuit)	10		
Tyrosol	Model (aspargine/fructose)	51		
	Food (biscuit)	17		
Chlorogenic acid (Phenol type) (0.5–50 μmol/ml)	Model (aspargine/glucose)	–	160 °C for 5–20 min	Cai et al. 2014
Chlorogenic acid (Quinone type)		Up to 55		
Homo orientin (10^{-6}-10 mmol/L)	Model (low moisture aspargine/glucose)	Up to 70	180 °C for 15 min	Zhang and Zang, 2008
Epigallocatechin gallate		Up to 70		

Besides pure phytochemicals with antioxidant activity, there are different reports about the effects of some plants and herbal extracts as additives on acrylamide mitigation. Most of these effects are attributed to phytochemicals with antioxidant power, carbonyl trapping activity, amino acid precipitation effect, and other supposed mechanisms of action. For example, there are significant positive correlations between DPPH-scavenging capacity (0.992) and reducing power (0.955) of some spices and their potency to reduce acrylamide formation (Jin et al. 2013; Salazar et al. 2012a; Zhu et al. 2011; Ciesarova et al. 2008; Cheng et al. 2010). Tables 2 and 3 have summarized some studies about natural compounds and medicinal plant effects on acrylamide content mitigation in model systems or foods.

Toxicity of Acrylamide

As mentioned in previous parts, acrylamide has been used as a chemical intermediate to produce polyacrylamide in different industries since the 1950s. Its toxic effects had been researched since then, but it specially attracted scientists' attention after 2002. They found that different foods, especially cereal based foods, which cooked at high temperatures, were the main source of human exposure to acrylamide. Different research studies confirmed that acrylamide and its biotransformed metabolite, glycidamide, are hazardous neurotoxins, reproductive toxins, and carcinogens in addition to their danger for other organs like the liver, kidney, intestines and lungs (Capuano and Fogliano 2011; Lopachin 2004).

Neurotoxicity

The proposed mechanisms for acrylamide neurotoxicity are central and peripheral nerve terminal degeneration, harmful effects on the cerebral cortex, thalamus and hippocampus, myodegeneration of muscles, decreasing release of neurotransmitter and interference with kinesin motor protein function and nerve signal transportation (Capuano and Fogliano 2011). Clinical manifestations of this toxicity are peripheral neuropathy, skeletal muscle weakness, numbness of movement organs, and ataxia. It has been typically concerned with occupational exposure, but recent studies have signalized the role of dietary exposure (CIAA 2011; Friedman and Levin 2008).

Reproductive toxicity

In this case, acrylamide can degenerate epithelial cells of seminiferous tubules and harmfully affect the number and shape of sperm, probably because of its interfering effects on kinesin motor protein in the flagella of sperm (Jin et al. 2013; Tyl and Friedman 2003; Tyl et al. 2000; Zhang and Zhang 2007a).

Carcinogenicity

Acrylamide was classified as a probable carcinogen for humans by the "IARC International Agency for Research on Cancer 1994 (Group 2A). National Toxicology and Report on carcinogens (2011) set acrylamide as "reasonably anticipated to be a human carcinogen". These classifications are supported by several studies, which show that acrylamide and glycidamide can form covalent adducts with DNA,

Table 3 Effect of medicinal plants on acrylamide content mitigation

Plant name	Used part	Acrylamide reduction (%)	Used system	Other parameters	References
Capsicum annuum L. var. Aviculare	Oleoresin of fruit (for frying)	– 26/77	Model (aspargine/glucose) Food (fried potato-5 min/ tortilla chips-2.30 min)	180 °C	Salazar et al. 2012a
Camellia sinensis (L.) Kuntze. *Rosmarinus officinalis* L. *Origanum vulgare* L.	Leaf (3 g/kg)	–	Olive Sterilization in computer controlled retort	121 °C for 15 min	Casado et al. 2010
Allium sativum L.	Blanched bulb (15 g/kg)	30.62			
	Raw (15 g/kg)	–			
Mentha canadensis L.	Aerial part	74.5	Model (aspargine/glucose)	180 °C for 15 min,Aqueous extract (0.1 mg /ml, 100 µl)	Zhu et al. 2009 Kotsiou et al. 2010 Arribas-Lorenzo et al. 2009 Arribas-Lorenzo and Morales 2012 Zhu et al. 2011
Cuminum cyminum L.	Seed	73.1			
Illicium verum Hook. f.	Fruit	68.9			
Coriandrum sativum L.	Seed	61.5			
Lycium barbarum L.	Fruit	60.1			
Eugenia caryophylata Thunb.	Bud	58.7			
Prunella vulgaris L.	Inflorescence	56.3			
Lens culinaris L.	Seed	55.6			
Capsicum frutescens L.	Fruit	55.5			
Vitis vinifera L.	Seed	54.1			
Citrus hystrix DC.	Leaf	50.7			
Murraya koenigii L.	Leaf	49.7			
Salvia officinalis L.	Aerial part	49.2			
Rheum officinalis Baill.	Root	48.7			
Foeniculum vulgare Mill.	Seed	48.1			
Rhus chinensis Mill.	Gall	47.6			
Petroselinum crispum L.	Leaf	47.5			
Camellia sinensis L.	Leaf	46.8			
Origanum vulgare L.	Leaf	46.1			
Chrysanthemum morifolium Ramat.	Flower	43.7			
Curcuma longa L.	Rhizome	42.2			
Fagopyrum esculentum Moench.	Grain	37.6			
Glycine max L.	Seed	36.9			
Gardenia jasminoides Ellis.	Fruit	35.8			
Cymbopogon citrates Stapf.	Stem	34.8			
Matteuccia strothiopteris (L.) Todaro.	Rhizome	32.9			
Myristica fragrans Houtt.	Fruit	31.7			
Punica granatum L.	Peel/Husk	30.1			
Rosa chinensis Jacq.	Flower	28.1			
Rubus chingii Hu.	Fruit	24.3			

Table 3 (continued)

Plant name	Used part	Acrylamide reduction (%)	Used system	Other parameters	References
Cinnamomum zeylanium N.	Cortex/Bark	23			
Acacia catechu (L.f.) Willd	Aerial part	22.7			
Morus alba L.	Fruit	14.5			
Crataegus pinnatifida Bge.	Fruit	11			
Ilex cornuta Lindl. et Paxt.	Leaf	–			
Olea europaea L.	Fruit virgin oil	–	Model (aspargine/glucose)	180 °C for 20 min, Phenolic extract	
Origanum vulgare L.	Leaf	49			
Olea europaea L.	Fruit virgin oil	Up to 20	Food (cooky)	190 °C for 16 min	
Allium cepa L.	Raw bulb	Up to 30	Food (cooky)	210 °C for 15 min, 0.25–4 % w/w	
Curcuma longa L.	Raw rhizome Aqueous extract	Up to 36 Up to 32	Food (cooky)	210 °C for 15 min	
Cuminum cyminum L.	Raw seed Aqueous extract	Up to 37 Up to 46	Food (cooky)	210 °C for 15 min	
Coriandrum sativum L.	Raw seed Aqueous extract	Up to 31 Up to 36	Food (cooky)	210 °C for 15 min	
Eugenia caryophylata Thunb.	Bud	Up to 56	Model (starch based)	190 °C for 20 min, 0.05–2 % w/w	
		Up to 50	Food (cooky)	210 °C for 15 min	
Cinnamomum zeylanium N.	Cortex/Bark	Up to 44	Model (starch based)	190 °C for 20 min	
		Up to 38	Food (cooky)	210 °C for 15 min	
Piper nigrum L.	Seed	50	Model (starch based)	180 °C for 20 min, Hydro- alcoholic extract	Ciesarova et al., 2008
Origanum majorana L.	Leaf	60			
Origanum vulgare L.	Leaf	60			
Pimenta dioica (L.) Merr.	Fruit	75			
Coriandrum sativum L.	Seed	–	Food (ginger cake)	180 °C for 18 min, powder 2% *w/w*	Markov et al., 2012
Cinnamomum zeylanium N.	Cortex/Bark	–			
Pimenta dioica (L.) Merr.	Fruit	–			
Illicium verum Hook. f.	Fruit	–			
Myristica fragrans Houtt.	Fruit	23			
Foeniculum vulgare Mill.	Seed	21			
Pimpinella anisum L.	Seed	17			
Eugenia caryophylata Thunb.	Bud	17			
Vanilla spp.	Seed	11			
Elettaria cardamomum (L.) Maton	Seed	9			
Piper nigrum L.	Seed	9			
Zingiber officinale Roscoe.	Rhizome	5			
Camellia sinensis L.	Leaf	43	Food (cooky)	190 °C for 7 min, Polyphenols (0.1 g/kg)	Li et al., 2012

Table 3 (continued)

Plant name	Used part	Acrylamide reduction (%)	Used system	Other parameters	References
*Phyllostachys nigra*var. *henonis* (Mitford) Stapf ex Rendle.		63.9		190 °C for 7 min, Antioxidants (0.2 g/kg)	
Malus domestica Borkh.	Fruit	35	Model (aspargine/glucose)	160 °C for 30 min, Ethanolic extract, 35 mg/ml, 2 ml	Cheng et al., 2010
Garcinia mangostana L.	Fruit	–			Abdel-Monem et al., 2013
Euphoria longana Lamk.	Fruit	–			
Hylocereus undatus (Haworth) Britton & Rose.	Fruit	–			
*Vaccinium corymbosum*L.	Fruit	–			
Phyllostachys nigra var. *henonis* (Mitford) Stapf ex Rendle.	Leaf	84.6	Food (potato chips)	190 °C for 7 min	
Psidium guajava L.		84			
Rosmarinus officinalis L.		85.7			
Origanum vulgare L.		92.8			
Olea europaea L.		75.7			
Vaccinium oxycoccos L.		59.6			
Camellia sinensis L.		56.5			
Phyllostachys nigra var. *henonis* (Mitford) Stapf ex Rendle.	Leaf	43.4	Model (aspargine/glucose)	180 °C, 10^{-6} mg/ml reaction solution	Zhang et al., 2008b
Camellia sinensis L.		32.3			
Olea europaea L.	Fruit virgin oil		Food (fried crisps)	180±1 °C for 5–15 min	Napolitano et al., 2008
*Phyllostachys nigra*var. *henonis* (Mitford) Stapf ex Rendle.	Leaf	Up to 74 Up to 76	Food (potato crisps) Food (French fries)	170±1 °C for 4 min, Antioxidants (0.001–1 % *w*/*w*)	Zhang et al., 2007a
*Phyllostachys nigra*var. *henonis* (Mitford) Stapf ex Rendle.	Leaf	Up to 59	Food (fried chicken wing)	170±1 °C for 4 min, Antioxidants (0.001–1 % *w*/*w*)	Zhang et al., 2007b
*Phyllostachys nigra*var. *henonis* (Mitford) Stapf ex Rendle.	Leaf	Up to 83	Food (bread)	180±3 °C (0.002–4.9 g of 30 % Hydro-alcoholic extract/kg flour)	Zhang and Zang, 2007b
Camellia sinensis L.		Up to 72.5			
Phyllostachys nigra var. *henonis* (Mitford) Stapf ex Rendle.	Leaf	Up to 74.4	Model (low moisture aspargine/glucose)	180 °C for 15 min (10^{-6}–10 mg/ml of antioxidants extract)	Zhang and Zang, 2008
Camellia sinensis L.		Up to 74.3			
Amaranthus hypochondriacus L.	Seed flour Seed protein	– Up to 40	Model (aspargine/glucose)	180 °C for 10 min (0–55 mg)	Salazar et al., 2012b
	Seed flour Seed protein	–	Food (cooky)	190 °C for 7–9 min (8 g)	
	Seed flour Seed protein	– –	Food (tortilla chips)	190 °C for 30–45 s or 205 °C for 4–5.25 min (5 % w/w)	
Rosmarinus officinalis L.	Leaf	Up to 38	Food (deep fried potato)	180 °C for 5 min (1,000 mg/kg of extract)	Urbancic et al., 2013

hemoglobin, and different functional groups of proteins like SH, inducing gene mutation and chromosomal aberration, increasing benign and malignant neoplasm in rodents (Casado et al. 2010; Kalita et al. 2013; Pelucchi et al. 2011; Salazar et al. 2012a; Zhu et al. 2010).

A current meta-analysis of epidemiologic study about acrylamide exposure and human cancers concluded that the risk of cancer does not increase by dietary or occupational exposure to acrylamide except for kidney cancer. This study attributed the risk underestimation to the low sensitivity of epidemiologic studies to detect a small increase in risk, exposure misclassification, and other methodological limitations and biases. It finally justified actions aimed at reducing human exposure to acrylamide and recommended further studies especially on kidney cancer (Yuan et al. 2011; Rice 2005). Figure 1 describes some subsequent intracellular events of acrylamide entrance to cells.

Effective natural compounds and phytomedicines against acrylamide toxicity

Regarding the importance of finding an effective way to constrain acrylamide hazards, several studies have been carried out to evaluate the plant extracts and the phytochemical effects on different aspects of acrylamide toxicity. Results of some studies about the beneficial effects of plants and their

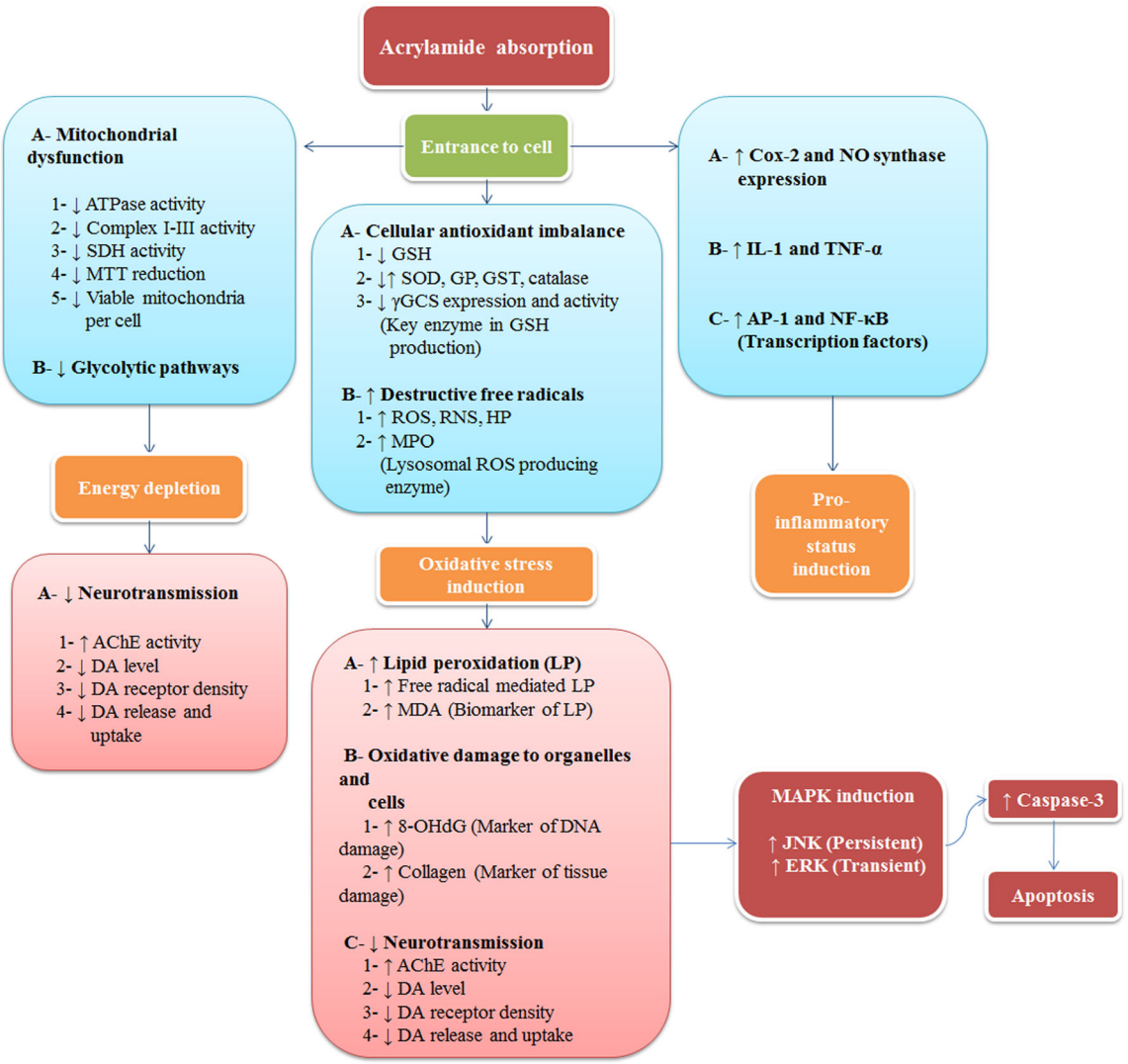

Fig. 1 Subsequent intracellular events of acrylamide entrance to cell, *AChE* AcethylCholin Esterase Activity; *AP*-1 Activator Protein 1; *COX*-2 Cyclooxygenase 2, *DA* Dopamine, *ERK* Extracellular Signal-Regulated Kinase, γ-GCS: γ-Glutamylcysteine Synthetase, *GSH* Glutathione; IL-1, Interleukin 1, *NK* c-Jun N-terminal Kinase, *MAPK* Mitogen-Activated Protein Kinase, *MDA* Malondialdehyde, *MTT*, Methylthiazol Tetrazolium Assay, 8-*OHdG*, 8-Hydroxydeoxyguanosine, *NF*-κB, Nuclear Factor kappa B, *RNS*, reactive nitrogen species, *ROS*, reactive oxygen species, *SDH* Succinate Dehydrogenase, *SOD* Superoxide Desmutase, *TNF*-α: Tumor Necrosis Factor Alpha

Table 4 Effective natural compounds and medicinal plants against acrylamide neurotoxicity

Treatment	Used part	Model	Significant effects of treatment on acrylamide toxicity	Proposed mechanism of action	References
Acorus calamus L.	Hydroalcoholic extract of rhizome (25 mg/kg)	Rat	Decreasing hind limb paralysis, recovery of motor behavioral parameters, increase GSH content in corpus striatum	Detoxification with GSH	Shukla et al., 2002
Panax ginseng C.A.Mayer	Standardized extract (20 mg/kg)	Rat	Recovery of brain antioxidant biochemical parameters like SOD activity	Inhibiting lipid peroxidation, increase SOD activity and free radical scavenging	Mannaa et al. 2006
Zingiber officinale Roscoe.	Ethanolic extract of rhizome (0.25 mg)	Mice	Improving histological structure of the nervous tissues in the spinal cord and cerebellum,	Decrease of lipid peroxidation, Detoxification with GSH	El-Tantavi, 2007
Glycin max (L.) Merr.	Dark soy sauce (0.5 ml/kg)	Rat	Improving body weight gain, relative brain weight, gait abnormalities, axonal degeneration and brain biochemical parameters like SOD activity	Antioxidant activities	Xichun and Minai, 2009
Genistein	Pure compound (25,50 mg/kg)	Rat	Decreasing oxidative stress and neuron injuries and apoptosis	Antioxidant and anti- apoptotic activities	Cheng-mei et al., 2009
Allium sativum L.	Powder (1.5 % w/w)	Rat	Decreasing total lipids and triglycerides and NO contents and increase phospholipids and GSH contents and SOD, GP, CAT and GST activity, decrease MAO activity and TBARS in brain	Detoxification with GSH, antioxidant activities, increasing neurotransmission due to inhibition of MAO activity	Ghareeba et al., 2010
Swietenia mahagoni L.	Methanolic extract of leaf (100,200 mg/kg)	Rat	Decreasing neuropathy and oxidative stress markers like TBARS, increase GSH, inhibit histopathological changes in sciatic nerve like axonal degeneration and derangement of nerve fibers	Detoxification with GSH, antioxidant activities	Vanitha et al. 2012
Crocus sativus L.	Purified crocin from stigma (10,20,50 μM)	PC12 cell line	Decreasing cytotoxicity, DNA fragmentation, Bax-Bcl-2 ratio, cell apoptosis and intracellular ROS (with 50 μM)	Antioxidant and anti-apoptotic activities	Mehri et al., 2012
Epigallocatechin-3 -gallate	Pure compound (5–100 μmol/L)	CGN cell line	Decreasing cytotoxicity, Bax-Bcl-2 ratio and cell apoptosis, increase SOD activity	Antioxidant and anti- apoptotic activities	Liu et al. 2012
Eugenol soeugenol	Pure compound (10,25 μM)	*Drosophila melanogaster*	Decreasing mortality, locomotor dysfunction and oxidative markers like MDA, ROS, PC and HP, increase GSH and dopamine content, modulate AChE activity in head region	Detoxification with GSH, antioxidant activities, increase of neurotransmission and anti-apoptotic activity due to inhibiting AChE	Prasad and Muralidhara, 2012
Eugenol Isoeugenol	Pure compound (10 mg/kg)	Rat	Decreasing oxidative markers like MDA, ROS and HP, AChE activity and Ca^{2+} and NO content in brain and sciatic nerve, increase GSH and DA content and ATPase activity in brain and sciatic nerve, increase feed intake, body weight, restore gait abnormalities	Detoxification with GSH, antioxidant and anti-inflammatory activities	Prasad and Muralidhara 2013
Bacopa monnieri (L.) Pennell.	Ethanolic extract of leaf (2–6 μg/ml)	N27 neuronal cell line	Restoring cell loss and GSH depletion	Detoxification with GSH, antioxidant activities	Shinomol et al., 2013
	Ethanolic extract of leaf (0.05 % v/w)	*Drosophila melanogaster*	Improving locomotor dysfunction and GSH depletion in head		
	Ethanolic extract of leaf (2 %)	Mice	Restoring brain oxidative damage and GSH depletion		

Table 4 (continued)

Treatment	Used part	Model	Significant effects of treatment on acrylamide toxicity	Proposed mechanism of action	References
Chrysin	Pure compound (0.5–5 μM) Pure compound (12.5,25,50 mg/kg)	PC12 cell line Rat	Decrease in cytotoxicity Improving gait abnormalities (with 50 mg/kg)	Antioxidant and anti-apoptotic activities	Mehri et al. 2014
Geraniol	Pure compound (5,10 μM)	*Drosophila melanogaster*	Decrease mortality and locomotor deficits, oxidative markers like MDA, ROS, HP and AChE activity, increase activity of antioxidant enzymes like TRR, GST, SOD and CAT, increase GSH, TSH and dopamine content, modulate HP and mitochondrial dysfunction in head and body regions	Antioxidant and neurogenerative activities, detoxification with GSH, increase neurotransmission and anti-apoptotic activity due to inhibit AChE	Prasad and Muralidhara 2014
Curcumin					

PC Phytochemical, *GSH* Glutathione, *SOD* Superoxide dismutase, *TBARS* Thiobarbituric acid reactive substance, *ROS* Reactive oxygen species, *AChE* Acetylcholinesterase, *MDA* Malondialdehyde, *HP* Hydroperoxides, *MAO* Monoamine oxidase, *NO* Nitric oxide, *DA* Dopamine, *TSH* Total thiol, *TRR* Thioreduxine reductase, *PC* Protein carbonyls

phytochemicals on acrylamide, showed induced toxicity in different models. These results are summarized in Table 4. According to these data, increasing reduced glutathione, inhibiting reactive oxygen species formation and oxidative stress, and reducing cell apoptosis are general proposed mechanisms for protective activities of phytoconstituents against acrylamide toxicity.

Tables 5 and 6 exhibit the most reported medicinal and food plants as well as natural compounds against different aspects of acrylamide related toxicity.

Discussion

Today, there is no doubt that antioxidants and other phytochemicals play considerable roles in either the prevention and cure of several illnesses, or reduction of toxicity induced by chemicals or environmental factors (Kahkeshani et al. 2013; Rahimi et al. 2005; Manayi et al. 2014; Mostafalou and Abdollahi 2013; Saeidnia and Abdollahi 2013a,b; Saeidnia and Abdollahi 2012). In this review, we aimed to focus on two important roles of antioxidants and phytochemicals on the reduction of acrylamide in food resources, and its toxicity in animals and humans as well.

Reduction of acrylamide content in foods

Among the various mechanisms by which chemicals are supposed to mitigate acrylamide from food sources, free radical scavenging activity is outstanding, particularly in the case of using phytoceuticals like polyphenols or plant derived antioxidants (Jin et al. 2013; Kalita et al. 2013; Salazar et al. 2012a,b; Zhu et al. 2010). An appraisal on Table 2, which summarized the findings of several studies on potentially active antioxidant compounds and acrylamide reduction, reveals that phenolic acids like *p*-coumaric acid, gallic acid, ferulic acid and caffeic acid could reduce the acrylamide content close to half or even lower (Abdel-Monem et al. 2013; Kotsiou et al. 2011; Zhu et al. 2009). The predominant hypothesis is that antioxidant compounds can decrease acrylamide formation but as mentioned in previous parts, there is still a controversy about correlation of acrylamide content and antioxidant activity in some cases. This problem can be explained considering the acrylamide formation reaction, which is partly complex. Acrylamide is produced in a series of multiple steps reactions between asparagine and a carbonyl compound with production of different intermediates. Thus, antioxidant compounds can interfere in various parts of this reaction according to their molecular structure and functional groups, and this interference can increase or decrease acrylamide production regardless of antioxidant activity (Jin et al. 2013).

As mentioned previously, an example is curcumin, which changes acrylamide content contrary to its antioxidant activity

Table 5 Effective natural compounds and medicinal plants against acrylamide-related reproductive toxicity, genotoxicity, and general toxicity

Treatment	Used part	Model	Significant effects of treatment on acrylamide toxicity	Proposed mechanism of action	References
Reproductive toxicity					
Phenylethyl isothiocyanate	Pure compound (0.5 %)	Rat	Decrease exfoliation of immature spermatocytes into the lumen of seminiferous tubules and degeneration of tubules	Inhibit CYP2E1 and acrylamide conversion to glicydamide in testis	Lee et al., 2005
Camellia sinensis (L.) Kuntze.	Water extract of leaf (70 mg/kg)	Rat	Restore serum testosterone level and harmful histopathological changes in testis like tubular endothelium thickening, germ cell degeneration, atrophy of semeniferous tubules and production of multinucleated giant cells	Antioxidant activity in serum, liver and testicular level	Yassa et al., 2013
Genotoxicity					
Aloysia triphylla (L'Her.) Britton	Water extract of leaf (5 %)	Mice	Decrease genotoxicity, increase total antioxidant capacity in plasma	Antioxidant activity due to polyphenols, decrease acrylamide epoxidation or detoxification of glicylamide	Zamorano-Ponce et al., 2006
General toxicity					
Azadirachta indica A.Juss	Ethanolic extract of leaf (200 mg/kg)	Rat	Restore GSH, MDA and CAT in liver and modulate histological injuries in liver, kidney, lung, heart, spleen and stomach	Detoxification with GSH, Antioxidant and anti- inflammatory activities	Mogda et al., 2008
Camellia sinensis (L.) Kuntze.	Extracted catechins (1.5 %)				
Resveratrol	Pure compound (30 mg/kg)	Rat	Decrease ALT, AST, LDH, BUN, creatinine, TNFα, IL-1, IL-6 and indicator of DNA damage, 8-OHdG, in serum, increase GSH and decrease collagen, MDA and MPO in brain, lung, liver, kidney and testis	Inhibit neutrophil infiltration, antioxidant and anti -inflammatory activities, Detoxification with GSH	Alturfan et al., 2012
Carica papaya L.	Water extract of fruit (250 mg/kg)	Rat	Decrease MDA and increase GSH, SOD and CAT in stomach, liver and kidney tissues	Detoxification with GSH, Antioxidant activity due to flavonoids and phenolic acids	Sadek, 2012
Allium sativum L.	2.5,5 %	Rat	Decrease MDA and increase GSH, SOD and in kidney, spleen, testis and brain, decrease urea, creatinine, LDH and alkaline phosphatase and increase total protein and albumin in serum	Detoxification with GSH, antioxidant activities	El-Halim and Mohamed, 2012
Solanum nigrum L.	Leaf and fruit powder (2 g/kg of diet)	Rat	Decrease mortality, urea, creatinine, LDH, ALT and AST, improve weight gain, total protein, albumin and globulin, IgG, IgM,	Antioxidant activity due to flavonoids and phenolic acids	Soliman, 2013
Cyanidin-3-glucoside	Pure compound (10–100 μM)	MDA-MB-231 cell line	Decrease cytotoxicity, LDH leakage, ROS formation, oxidative stress, GSH depletion and GST and GP activity, increase GPx1 and GSTP1 and decrease CYP2E1expression, increase γGCS expression as a marker of GSH synthesis	Detoxification with GSH, antioxidant activities, Inhibit CYP2E1 and acrylamide conversion to glicydamide	Song et al., 2013
Allium sativum L. *Hibiscus sabdariffa* L.	Powder (54 mg/kg) Powder (81 mg/kg)	Rat	Restore serum triglyceride, cholesterol, HDL, SOD, GP and CAT	Antioxidant activity due to allicin, ascorbic acid, flavonoids, anthocyanins and phenolics	El-Shafey et al., 2013
Allicin	Pure compound (5,10,20 mg/kg)	Mice	Decrease TBARS and MPO and increase SOD and GSH in kidney, liver and brain, decrease ALT, AST, LDH, BUN, TNFα, IL-1, IL-6 and ROS and increase IL-10 in serum	Detoxification with GSH, antioxidant activities	Zhang et al., 2013

LDH Lactate dehydrogenase, *ROS* Reactive oxygen species, *GSH* Glutathione, *GST* Glutathione-S-Transferase, *GP* Glutathione peroxidase, *ALT* Alinine transaminase, *AST* Aspartate transaminase, *MDA* Malondialdehyde, *OD* Superoxide dismutase, *CAT* Catalase, *MPO* Myeloperoxidase, *BUN* Body urea nitrogen, *TNF* Tumor necrosing factor, *IL* Interleukin, *γGCS* Gamma-glutamyl cysteine synthase, 8-*OHdG* 8-Hydroxydeoxyguanosine

Table 6 Effective natural compounds and medicinal plants against acrylamide-related intestinal and hepatotoxicity

Treatment	Used part	Model	Significant effects of treatment on acrylamide toxicity	Proposed mechanism of action	References
Intestinal toxicity					
Hydroxytyrosol	Pure compound (5–40 μM)	Caco-2 cell line	Decrease LDH, ROS and apoptosis inducers like JNK and its active form p-JNK contents and caspase-3, GP and GR activity, increase cell viability	Antioxidant and anti-apoptotic activities due to polyphenols	Rodriguez-Ramiro et al., 2011a
Theobroma cocoa	Polyphenolic extract (10 μg/ml)	Caco-2 cell line	Decrease caspase-3 activity, cell apoptosis, GSH depletion and ROS formation, increase GST and γGCS activities, increase ERK and its active form p-ERK which favor survival signals and inhibit p-JNK increase (epichatechin is the weakest)	Antioxidant and anti-apoptotic activities due to polyphenols	Rodriguez-Ramiro et al., 2011b
Epicatechin	Pure compound (10 μM)				
Procyanidin B2	Pure compound (10 μM)				
Solanum	Raw fiber (2 %) Heated fiber (2 %)	Mice	Increase mitotic number,improve number of proliferating cells and decrease number of apoptotic cells in intestine epithelium, improve histomorphology parameters of epithelium, submucosa, mucosa and neurofilaments especially intestine absorptive surface (higher activity with heated form)	Reduction of chemical absorption due to binding them and enhance fecal passage	Dobrowolski et al., 2012; Woo et al., 2007
Myrcitrin	Pure compound (2.5–10 μg/ml)	Caco-2 cell line	Increase cell viability, attenuate intracellular ROS	Antioxidant activity and decrease oxidative stress	Chen et al., 2013
Hepatotoxicity					
Hydroxytyrosol	Pure compound (12.5-50 μM)	Hep-G2 cell line	Decrease micronucleus frequency, genotoxicity and ROS formation, prevent GSH depletion, enhance γGCS expression	Detoxification with GSH, antioxidant activities	Zhang et al., 2008a
Curcumin	Pure compound (2.5 μg/ml)	Hep-G2 cell line	Decrease cytotoxicity, ROS formation, DNA damage, micronucleus frequency,	Antioxidant activity especially against hydrogen peroxide	Cao et al., 2008
Hydroxytyrosol	Pure compound (12.5–50 μM)	Hep-G2 cell line	Increase cell viability, decrease DNA damage, ROS level, 8-OHdG as a marker of oxidative DNA damage and GSH depletion	Detoxification with GSH, antioxidant activities	Zhang et al., 2009a
Allium sativum L.	Powder (1.5 % w/w)	Rat	Decrease total lipids and triglycerides, TBARS and NO level, increase GSH and SOD, GP and GST activity in liver	Detoxification with GSH, antioxidant activities	Ghareeb et al. 2010
Honey	Aqueous solution (0.01–10 mg/ml)	Hep-G2 cell line	Increase cell viability	Antioxidant activity due to polyphenols	Mademtzoglou et al., 2010
Digera muricata	Methanolic extract (100,150,200 mg/kg)	Rat	Restore ALT, AST, ALP, LDH, BUN, cratinine, bilirubin, total protein and albumin, CAT, SOD, GP and GST	Antioxidant activity due to phenolics and flavonoids	Khan et al., 2011
Allicin	Pure compound (3.75,7.5,15 μM)	Mice hepatocyte	Decrease cytotoxiciy, MDA and 8-OHdG, increase GSH content and SOD activity	Detoxification with GSH, antioxidant activities, Inhibit CYP2E1 and acrylamide conversion to glicydamide	Zhang et al., 2012
	Pure compound (5,10,20 mg/kg)	Mice	Increase GSH content and SOD activity, decrease MDA and 8-OHdG contents		

LDH Lactate dehydrogenase, *ROS* Reactive oxygen species, *GP* Glutathione peroxidase, *GR* Glutathine reductase, *JNK* c-Jun N-amino terminal kinase, *ERK* Extracellular regulated kinase, *GSH* Glutathione, *GST* Glutathione-S-transferase, γGCS: Gamma-glutamyl cysteine synthase, 8-OHdG: 8-Hydroxydeoxyguanosine, TBARS: Thiobarbituric acid reactive substance, *CAT* Catalase, *BUN* Body urea nitrogen, *MDA* Malondialdehyde

because of its specific functional groups (Hamzalioglu et al. 2013). There are other factors rather than antioxidant structure, which can affect acrylamide content. For example, some phenolic acids like chlorogenic acid can convert sucrose into more reactive intermediates like 5-Hydroxymethylfurfural that reacts with aspargine with more tendency, and increases acrylamide production (Kocadagl et al. 2012). On the other hand, some flavonoids like naringenin or epicatechin decrease acrylamide production through reaction with different intermediates of Maillard reaction and trapping them (Cheng et al. 2009; Totlani and Peterson 2005; Totlani and Peterson 2006).

Jin et al. (2013) have comprehensively discussed the relationship between antioxidants and acrylamide formation. They concluded that antioxidants can affect four parts of Maillard reaction: 1- reactive carbonyl pool as substrate, 2- asparagine as substrate, 3- intermediates and 4- acrylamide as product. Antioxidants can decrease or increase reaction between two substrates, and activate or deactivate them. Moreover, they can affect intermediates or final product, and change acrylamide production trend.

Different studies showed that increasing concentration of antioxidant couldn't mitigate acrylamide formation in all cases and sometimes the higher concentration surprisingly increased acrylamide production (Kotsiou et al. 2010; Yuan et al. 2011; Zhu et al. 2010).

In addition to the role of antioxidants and their structures, other parameters related to reaction condition like temperature and heating time, pH and moisture can dramatically affect acrylamide content. This highlights the importance of usage the standard model systems with defined reaction condition for experiments (Jin et al. 2013).

Among a number of medicinal plants subjected to investigations (in different studies) for reducing the acrylamide content in food, *Mentha canadensis*, *Phyllostachys nigra*, *Pimenta dioica*, *Illicium verum*, *Camellia sinensis*, *Origanum vulgare* and *Olea europaea* exhibited considerable mitigation activity (Abdel-Monem et al. 2013; Zhang et al. 2007a,b; Zhu et al. 2009). Previous studies showed that in some cases, crude aqueous extracts were able to inhibit acrylamide formation more than their pure constituents especially poly phenols. Therefore, beside poly phenolic compounds, other phytochemicals might play role in mitigation of acrylamide not only by free radical scavenging activity but also by other mechanisms like trapping carbonyl moiety or/and precipitating aspargine and constituents like proteins, peptides, saccharides and monovalent/divalent cations (Oral et al. 2014; Cheng et al. 2010; Zhu et al. 2009; Zhu et al. 2010).

Reduction of acrylamide toxicity

Tables 4 and 6 show that plants with high contents of polyphenols and antioxidant activity like *Theobroma cocoa*, *Solanum nigrum*, *Panax ginseng*, *Digera muricata*, *Crocus sativus*, *Glycin max*, and *Zingiber officinalis*, as well as antioxidant compounds like myrcitrin, genistein, resveratrol, and curcumin have been reported to be effective in the reduction of acrylamide toxicity in cell lines and/or animal studies. Although the proposed mechanisms of action for each plant extract or phytochemical are illustrated in Tables 4 and 6, it seems that most of them may act via multiple mechanisms such as anti-apoptotic and anti-inflammatory activities (Zhang et al. 2007a a,b).

Conclusion

- Acrylamide, which can be formed in fried and baked foods due to high temperatures, is demonstrated to be a source of different toxicities in animals and humans.
- There are some chemicals exhibiting mitigation activity to reduce the acrylamide contents in food, of which phytoceuticals and phytomedicines have been studied and proved to possess such activity via different mechanisms, such as free radical scavenging activity.
- Beside the positive role of antioxidants in acrylamide reduction in food, the exact role of antioxidants in this regard is still under question due to some controversial reports.
- Antioxidative activity is one of the probable mechanisms, by which phenolic-containing herbal medicines are able to reduce the acrylamide toxicity in both in vitro and in vivo studies, although other mechanisms such as anti-apoptotic, anti-inflammatory, and the reduction of chemical absorption due to enhanced fecal passage are suggested.

Acknowledgments This paper is the outcome of a financially non-supported study. Special thanks to Miss Sherlin Haghnazari for revising the English language of this article.

Conflict of interest statement Authors have no competing interests.

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