Role of polyphenols and nonpolyphenols against toxicity induced by fluoride: a comprehensive review

Article *in* European journal of cancer prevention: the official journal of the European Cancer Prevention Organisation (ECP) · April 2018

DOI: 10.1097/CEJ.0000000000000424

8 authors, including:

Bianca Andrade Handan
Universidade Federal de São Paulo
7 PUBLICATIONS **41** CITATIONS
SEE PROFILE

Carolina Foot Gomes de Moura
Universidade Federal de São Paulo
32 PUBLICATIONS **430** CITATIONS
SEE PROFILE

Milena B Viana
Universidade Federal de São Paulo
80 PUBLICATIONS **2,536** CITATIONS
SEE PROFILE

Liria yuri Yamauchi
Universidade Federal de São Paulo
17 PUBLICATIONS **67** CITATIONS
SEE PROFILE

Role of polyphenols and nonpolyphenols against toxicity induced by fluoride: a comprehensive review

Samuel R. Claudio[a], Bianca A. Handan[b], Carolina F. Gomes de Moura[b], Milena de Barros Viana[b], Liria Y. Yamauchi[c], Odair Aguiar Jr[b], Celina T.F. Oshima[a] and Daniel A. Ribeiro[a]

Since its discovery as an antimicrobial agent, fluoride has been used in the control of dental caries. Many studies have shown that the chronic exposure of fluoride in high concentrations causes adverse effects in multiple organs; the use of bioactive compounds present in foods as a tool to mitigate the effects of fluoride could potentially be useful for populations in different parts of the world are exposed to fluoride in a chronic and systemic way. Thus, the aim of this comprehensive review is to present and discuss the published papers that focused on the use of polyphenols and nonpolyphenols that can mitigate the harmful activities promoted by fluoride exposure. Certainly, these data will contribute toward a better understanding of the role of food compounds in the pathological outcomes induced by fluoride. The new information will be added to that already available for regulatory purposes as a safe way to promote oral healthcare and prevent oral carcinogenesis. ***European Journal of Cancer Prevention*** **00:000–000**

European Journal of Cancer Prevention 2018, **00**:000–000

Keywords: fluoride, polyphenols, toxicity

Departments of [a]Pathology, [b]Biosciences and [c]Human Movement Sciences, Federal University of São Paulo, UNIFESP, Santos, Brazil

Correspondence to Daniel A. Ribeiro, DDS, PhD, Department of Biosciences, Federal University of São Paulo, UNIFESP, Av. Ana Costa, 95, Vila Mathias, Santos 11060-001, Brazil
Tel: +55 133 878 3774; fax: +55 132 290 100; e-mail: daribeiro@unifesp.br

Received 23 February 2017 **Accepted** 13 July 2017

Introduction

Since its discovery as an antimicrobial agent, fluoride has been used in the control of dental caries. As the procedure of fluoridation involves low cost, fluoride has been added to several sources such as toothpaste, water, restorative materials, and mouthwash (Petersen *et al.*, 2008). Fluoride was also added to soft drinks, juices, and beverages. It is undeniable that this ion has promoted oral health worldwide; however, it is known that the general population is being exposed to high concentrations of fluoride.

In recent decades, with the advancement of public health policies for the control of dental caries, several countries have expressed some concern in terms of the considerable exposure to fluoride, especially in developed countries. This is because of the fact that several studies have shown that chronic exposure to fluoride exerts adverse effects on oral tissues. For example, exposure to fluoride interferes with odontogenesis, which in turn promotes damage to the dental enamel at high concentrations (Ribeiro *et al.*, 2006). In addition, it has been shown that fluoride can promote bone loss (Junrui *et al.*, 2016). This condition is called fluorosis.

With an increasing knowledge of the consequences of systemic exposure of fluoride, it has been shown that other organs over mineralized tissues are highly affected by fluoride exposure, such as the liver, kidney, heart, and central nervous system (Goodarzi *et al.*, 2016). Such pathobiological effects are mainly because of the induction of oxidative stress induced either by lipid peroxidation or by reduction of levels of antioxidant enzymes, such as catalase (CAT), and superoxide dismutase (SOD) or even by interference with the expression of xenobiotic metabolism enzymes such as for example gluthationes (Campos-Pereira *et al.*, 2017). Recent studies have confirmed that fluoride triggers the apoptotic process through the activation of caspases (Deng *et al.*, 2016). Release of cytochrome C and decreasing ATP synthesis were also observed (Suzuki *et al.*, 2015). Thus, in view of the chronic exposure to fluoride, in high concentrations in some countries, especially in developing nations, new strategies for preventing or even mitigating the adverse effects of fluoride are necessary not only to protect populations exposed to this condition but also for health professionals for understanding the real risks posed by systemic fluoride exposure. Today, fluoride is an environmental and industrial pollutant that affects various organs in humans and animals (Choubisa and Choubisa, 2016). It is alarming that fluoride has been categorized as an environmental carcinogen (Swenberg *et al.*, 1999).

Accumulating evidence suggests that a balanced nutrient-rich diet is necessary for promoting health (Shlisky *et al.*, 2017). In this context, many bioactive food compounds derived from polyphenolic and nonpolyphenolic origins

DOI: 10.1097/CEJ.0000000000000424

have been shown to be effective as potential therapeutic agents in various chronic degenerative diseases, such as hypertension, diabetes, and cancer. Polyphenols are natural compounds with variable phenolic structures; it is very common in vegetables, fruits, tea, and wine (Bravo, 1998). To date, 8000 polyphenol molecules have been described in the scientific literature (Cheynier, 2005). All polyphenols contain one or more aromatic rings with more than one hydroxyl group (Tsao, 2010). They are classified into four groups, because of the number of phenol rings and chemical groups bound to the rings, as follows: flavonoids, phenolic acids, stilbenes, and lignants (Tsao, 2010).

Therefore, the use of bioactive compounds present in foods as a tool to mitigate the effects of fluoride could potentially be useful for populations in different parts of the world exposed to this ion chronically. Thus, the aim of this comprehensive review is to present and discuss the published papers that have focused on the use of polyphenols and nonpolyphenols that can mitigate the harmful activities promoted by fluoride exposure. Certainly, these data will contribute toward a better understanding of the role of food compounds in the pathological outcomes induced by fluoride.

Materials and methods

A comprehensive literature search for studies on 'fluoride, food, compounds, diet, polyphenols' was performed in the last 10 years. In brief, a search of PubMed, Medline, Embase, and Google Scholar was carried out for a variety of articles (all publications until January 2017). Case reports and papers not written in the English language were excluded from the review. All papers were identified and included in this review.

Results

After searching the scientific literature, we identified many studies investigating the role of food bioactive compounds derived from polyphenolic and nonpolyphenolic origins against fluoride toxicity. Below, we critically describe and explain the nature of these studies in detail.

Polyphenols

Flavonoids

Rutin, also called rutoside, quercetin-3-O-rutinosideandsophorin, is the glycoside combining the flavonol quercetin and the disaccharide rutinose [α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranose]. It is a citrus flavonoid found in a wide variety of plants such as citrus fruits. Treatment with rutin effectively decreased the genetic damage induced by fluoride exposure in rat heart cells (Umarani *et al.*, 2015). Epigallocatechingallate (EGCG), which is a green tea catechin found in a variety of green tea preparations, also decreased DNA fragmentation and inhibited proapoptotic markers in rat heart after exposure to fluoride (Miltonprabu and Thangapandiyan, 2015). In the rat liver, administration of EGCG restored the histopathological damage and biochemical indices and prevented DNA damage induced by fluoride (Thangapandiyan and Miltonprabu, 2013).

The levels of antioxidants enzymes such as CAT, SOD and glutathione (GSH) increased whereas the lipid perioxidation product decreased after rutin treatment in the rat heart exposed to fluoride (Umarani *et al.*, 2015). Moreover, EGCG increased the levels of mitochondrial enzymes such as ICDH, SDH, MDH, α-KGDH, and NADH in rat heart cells (Miltonprabu and Thangapandiyan, 2015). The same observations were made in the liver (Thangapandiyan and Miltonprabu, 2013). In-vitro studies using hepatocytes have shown that EGCG provides significant cellular protection against oxidative stress induced by excessive fluoride by means of iron metabolism regulation as a result of glutathione peroxidase (GSH-Px) content, SOD activity, and total antioxidant capacity levels (Niu *et al.*, 2016). At the molecular level, EGCG also inhibited Keap1 protein by the activation of Nrf2 translocation into the nucleus in lung cells (Shanmugam *et al.*, 2016). In summary, EGCG potentially abrogates Fl-induced oxidative lung injury by activation of the Nrf2/Keap1 pathway in rats (Shanmugam *et al.*, 2016). Therefore, it is assumed that rutin and EGCG have free radical scavenging and antioxidant activities, which protect rats against NaF-induced oxidative damage.

Anthocyanins are polyphenols and well known for their biological antioxidant benefits. The treatment with maize purple plant pigment rich in anthocyanins reduced the malondyaldehyde levels in blood and liver, and increased the SOD and GSH-Px activities in the kidney and GSH levels in the liver and kidney of rats exposed to increasing concentrations of fluoride (Zhang *et al.*, 2014). In addition, maize purple plant pigment decreased Bcl-2 protein expression and increased Bax protein expression induced by fluoride (Zhang *et al.*, 2014). Blackberry juice containing anthyocyanins decreases SOD, CAT and GSH, TBARS, nitric oxide, total lipids, cholesterol, triglucerides, plasma transaminases and creatine kinease levels in rat hepatic cells exposed to fluoride. Therefore, bioactive compounds found in blackberry juice promoted free radicals scavenging, which led to improved endogenous antioxidant status (Hassan and Yousef, 2009). It seems that anthocyanins protect against fluoride toxicity by interfering with both the apoptotic process and oxidative stress induced by fluoride.

Quercetin effectively reduced the levels of thiobarbituric acid-reactive substances and restored the activities of antioxidant enzymes in the liver, kidney, testis, and brain of rats (Hamza *et al.*, 2015; Nabavi *et al.*, 2012a,b). Moreover, quercetin prevented tissue degeneration (Hamza *et al.*, 2015). The same results were observed in rat brain exposed to NaF. Similar results were found on using a combination of quercetin and blackberry extract following high fluoride exposure (Hamza *et al.*, 2015). The levels of antioxidant enzymes, such as SOD and

CAT, GSH, and lipid peroxidation, were modulated in the cardiac tissue of animals intoxicated with fluoride and treated with quercetin (Nabavi *et al.*, 2012b). Certainly, quercetin protected rat heart tissue from the oxidative stress induced by fluoride by means of antioxidant activity (Nabavi *et al.*, 2012a).

Until rare bio products, such as methyl-3-O-methyl gallate (M3OMG), were able to exert some positive action against toxicity induced by fluoride in rat erythrocytes. Rats exposed to NaF with M3OMG protected against NaF-induced oxidative stress (Nabavi *et al.*, 2013b). The same findings were obtained for the brain as M3OMG treatment mitigated the NaF-induced oxidative stress through normalization of the level of TBARS and decreasing GSH activities (Nabavi *et al.*, 2013b).

Ginkgo biloba extract has been studied extensively in patients with neurological disorders such as Alzheimer's disease and Parkinson's disease. Some studies have shown that *G. biloba* improves learning and memory abilities, enhances the activities of SOD and ghutationes, attenuates the level of MDA, upregulates the ratio of Bcl-2/Bax, and downregulates the level of cleaved caspase 3 in rats exposed to high concentrations of fluoride (Zhang *et al.*, 2013). *G. biloba* could also prevent spatial learning and memory deficits in rats (Jetti *et al.*, 2016).

Pomegranates contain a complex mixture of gallotannins, ellagitannins, ellagic acid, and anthocyanins. To investigate the protective effects of pomegranate (*Punica granatum*) juice (PGJ) on the oxidative damage induced by fluoride in hepatocytes and erythrocytes (Bouasla *et al.*, 2016), some authors pointed out that the administration of PGJ juice led to the re-establishment of the oxidative status, indicating that PDJ is useful for preventing oxidative damage induced by NaF (Bouasla *et al.*, 2016).

Silymarin administration to animals before NaF consumption also altered the levels of biochemical parameters (Nabavi *et al.*, 2012c). Particularly, there was a significant increase in the levels of thiobarbituric acid-reactive substances, along with a decrease in antioxidant enzyme activity (SOD and CAT), and a decrease in the GSH level in the tissues exposed to high concentrations of fluoride *in vivo* (Nabavi *et al.*, 2012c).

Averrhoa carambola L. fruit (star fruit) is very consumed fruit in tropical countries and is an ingredient in folklore medicines. As the fruits have high polyphenolic and antioxidant contents, some authors have investigated whether some fruits protect against fluoride toxicity (Vasant and Narasimhacharya, 2012). A 4-week exposure to fluoride induced sustained hyperglycemia, hyperlipidemia, and oxidative stress. When animals were treated with a diet rich with star fruit, the lipid and antioxidant statuses were restored significantly (Vasant and Narasimhacharya, 2012). These findings suggest that star fruit can be used as a dietary supplement in fluoride-endemic regions exposed to high concentrations of fluoride (Vasant and Narasimhacharya, 2012).

According to a phytochemical analysis, tamarind fruit contains phenolic compounds such as catenin, procyanidin B2, epicatechin, tartaric acid, mucilage, pectin, arabinose, xylose, galactose, glucose, uronic acid, and triterpen (Harborne and Williams, 1992). Tamarind extract treatment decreased fluoride content and oxidative status [reactive oxygen species (ROS) generation, lipid peroxidation, protein carbonyl content, and nitric oxide] and improved antioxidant activity (SOD, CAT, GSH-Px and GSH) in lung epithelial cells (Ameeramja *et al.*, 2016). Furthermore, tamarind fruit modulated fluoride-activated changes in the mitochondrial membrane potential, permeability transition pore opening, cytochrome-C release, Bax/Bcl-2 ratio, and caspase-3 and PARP-1 expressions. In conclusion, these data showed that tamarind fruit could potentially be protect against fluoride toxicity, and may be utilized as a nutraceutical agent (Ameeramja *et al.*, 2016).

Stilbenes

Stilbenes are mainly found in plants and they are important phytochemicals against fungal infection. The most important stilbene investigated in the literature is resveratrol. A search of the literature showed that resveratrol restored antioxidant status, biogenic amine level and structural organization of rat brain exposed to high concentrations of fluoride (Atmaca *et al.*, 2014). Such findings suggest that resveratrol is an antioxidant agent in different regions of brain (Atmaca *et al.*, 2014; Pal and Sarkar, 2014). The same findings were obtained in rat liver (Atmaca *et al.*, 2014). For blood tissue, resveratrol also improved aminotransferase enzyme activity and inorganic phosphorus levels (Atmaca *et al.*, 2014).

Phenolic acids

It has been established that phenolic acids have strong anticancer activity (Anantharaju *et al.*, 2016). In particular, some studies have shown that a phenolic acid, such as gallic plays an important role against gastric cancer (Ho *et al.*, 2013). Other phenolic acids, such as the caffeic acid (CA), are considered active antioxidant agents (Chiou *et al.*, 2017).

In this review, CA significantly prevented hepatic damage induced by fluoride induced as shown by histopathological evaluation (Kanagaraj *et al.*, 2015). Some liver biomarkers' enzyme function also modulated by CA exposure (Kanagaraj *et al.* 2015). For example, a significant decrease in the levels of enzymatic (SOD, CAT, and ghutationes) antioxidants, along with increased ROS, lipid peroxidation, protein carbonyl content, and nitrate levels, were detected (Kanagaraj *et al.*, 2015).

Caffeic acid phenethyl ester (CAPE) protected endometrial tissue against damage induced by fluoride exposure by increasing antioxidant status in female rats. This

is because CAPE associated with fluoride treatments decreased MDA levels and increased SOD and CAT expression in endometrial tisue (Guney *et al.*, 2007).

Lignans

Sesamin, a major lignan derived from sesame seeds, has been reported to have many benefits and medicinal properties. Sesamin decreased the levels of p-JNK protein in the kidney, which in turn inhibited proapoptotic signaling events by restoring the balance between mitochondrial pro-apoptotic and anti-apoptotic Bcl-2 and Bax proteins, and by decreasing the release of mitochondrial cytochrome c in the kidney of fluoride-exposed fish (Cao *et al.*, 2015). JNK was also involved in the mitochondrial extrinsic apoptotic pathways of sesamin effects against fluoride-induced renal injury by regulating the levels of p-c-Jun, tumor necrosis factor-α, and Bak proteins (Cao *et al.*, 2015). These findings suggest that sesamin could protect kidney against fluoride-induced apoptosis by the oxidative stress downstream-mediated changes in the inactivation of the JNK signaling pathway. Taken together, sesamin plays an important role as a nutraceutical agent against fluoride toxicity in kidney cells (Cao *et al.*, 2015).

Other polyphenols

Curcumin is a polyphenol derived from *Curcuma longa* (turmeric plant). It belongs to the ginger family, which has long been used in Ayurvedic medicines to treat various diseases such as asthma, anorexia, coughing, hepatic diseases, diabetes, heart diseases, wound healing, and Alzheimer's disease (Di Martino *et al.*, 2017). Several studies have shown that curcumin has anti-infectious, anti-inflammatory, antioxidant, hepatoprotective, thrombosuppressive, cardio protective, antiarthritic, chemo preventive, and anti-carcinogenic actions (Qadir *et al.*, 2016). It was able to suppress the initiation–promotion of carcinogenesis (Qadir *et al.*, 2016). The anticancer activity of curcumin is because of the negative regulation of inflammatory cytokines, transcription factors, protein kinases, ROS, and oncogenes (Qadir *et al.*, 2016).

On searching the literature on the effects of curcumin on fluoride toxicity, the results showed that curcumin prevented neurodegeneration compared with those treated with fluoride in mice (Sharma *et al.*, 2014). Moreover, curcumin was antigenotoxic and antimutagenic by reducing the frequency of structural aberrations, hypoploidy, and primary DNA damage. Taken as a whole, curcumin mitigates the genotoxic effects induced by fluoride exposure *in vitro* (Tiwari and Rao, 2010). Animals treated with curcumin before NaF intoxication also showed a significant reduction in MDA levels. Also, pretreatment with curcumin restored the SOD and CAT activities and modified the level of reduced GSH compared with the control group (Nabavi *et al.*, 2012d). Moreover, curcumin normalized the levels of serum creatinine, serum urea, and blood urea nitrogen (Nabavi *et al.*, 2012e). Because of antigenotoxicity and antimutagenicity, curcumin also represents an antioxidant agent against fluoride toxicity.

Nonphenolic constituintes

Lycopene

Lycopene is a lipid-soluble powerful antioxidant that scavenges free radicals and ROS. It is plausible to consider that lycopene can be an effective antioxidant agent that can attenuate fluoride toxicity. To verify the effects of lycopene on NaF-induced teeth and ameloblast toxicity, rats were treated with fluoride for 5 weeks. The results indicated that the concentrations of fluoride, MDA and ROS, gene expressions and activities of caspase-9 and caspase-3, and the gene expressions of Bax were significantly decreased, whereas the expression of SOD and GSH-Px, and Bcl-2 were significantly increased after lycopene treatment (Li *et al.*, 2017). Concentrations of MDA and ROS, gene expressions and activities of caspase-9 and caspase-3, and the gene expression of Bax, and ameloblast apoptosis rate were significantly decreased, whereas the activities of SOD and GSH-Px, and the gene expression of Bcl-2 were significantly increased in rats treated with lycopene (Li *et al.*, 2017). These results suggest that lycopene significantly combated genotoxicity and cytotoxicity in ameloblasts by attenuating oxidative stress and downregulating the caspase pathway (Li *et al.*, 2017).

In other cellular types, lycopene increased the GSH level, total antioxidant capacity, and SOD activity in red blood cells, heart, and brain tissues after the administration of NaF. The induced oxidative stress and the alterations in the antioxidant system induced by fluoride exposure were normalized by the oral administration of lycopene treatment (Mansour and Tawfik, 2012).

Vitamins

The administration of vitamins C and E and fluoride treatment decreased MDA levels in endometrial tissue, whereas SOD, GSHs, and CAT activities increased (Guney *et al.*, 2007). Vitamins promoted tissue regeneration against fluoride-induced endometrial damage as well (Guney *et al.*, 2007). Lymphocyte and eosinophil infiltration in the stroma of rats treated with fluoride were more pronounced compared with that in nonexposed animals (Guney *et al.*, 2007). It can be concluded that oxidative endometrial damage plays an important role in fluoride-induced endometrial toxicity, and the modulation of oxidative stress with vitamins reduces fluoride-induced endometrial damage both at the biochemical and at the histological level (Guney *et al.*, 2007). Vitamin C improved SOD and CAT activities and modified the level of reduced GSH in rat liver cells exposed to high concentrations of fluoride (Nabavi *et al.*, 2012a).

Rats treated with vitamin C were protected against NaF-induced oxidative stress (Nabavi *et al.*, 2013a). Vitamin C

also protected against the behavioral deficits caused by fluoride (Jetti *et al.*, 2016). Taken together, chronic exposure to high levels of fluoride causes severe impairment in spatial learning and memory, these alterations being mitigated by vitamin C (Jetti *et al.*, 2016).

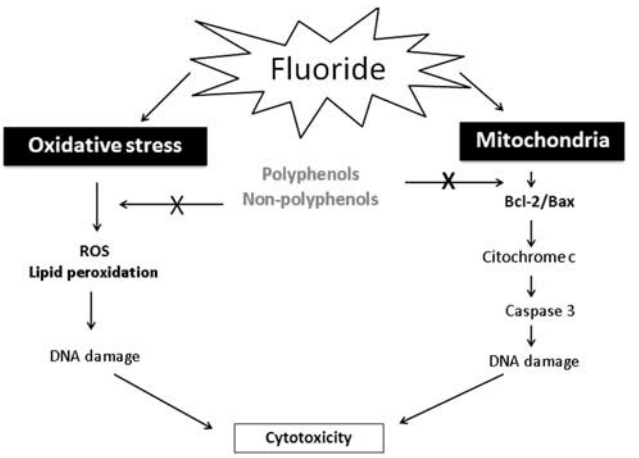
Other bioactive agents

Taurine is a free intracellular β-amino acid with antioxidant and neuroprotective properties. Hepatocytes exposed to taurine, in combination with NaF, increased the levels of the antioxidant enzymes such as SOD, CAT, and glutathione-S-transferase (Das *et al.*, 2008). There was a reduction of the level of GSH and total thiols and increased oxidatized glutathione, lipid peroxidation end products, protein carbonyl content and DNA damage (Das *et al.*, 2008). In the central nervous system, taurine exerted positive effects as it prevented NaF-induced increase in hydrogen peroxide and lipid peroxidation levels, but increased acetylcholinesterase and antioxidant enzyme activities in the hypothalamus, cerebrum, and cerebellum of the rats (Adedara *et al.*, 2017).

The beneficial effects of oleanolic acid on fluoride-induced oxidative stress and certain metabolic dysfunctions were investigated in rat brain. Fluoride increased the MDA level, free amino acid nitrogen, NO content, and free OH radical generation. In addition, fluoride increased GSH content and reduced SOD, GSH-Px, GR, and CAT activities in brain tissues. Oral supplementation of oleanolic acid improved brain metabolic functions significantly. The interesting effects of oleanolic acid against fluoride-induced changes in protein and nucleic acid contents, proteolytic enzyme activities, and other oxidative stress parameters indicate that oleanolic acid exerts potential antioxidative effects against fluoride-induced oxidative brain damage (Sarkar *et al.*, 2014).

The increased accumulation of fluoride in the brain observed in the NaF-treated group compared with the control was decreased in the selenium + NaF-treated group. Selenium levels increased in the selenium + NaF-treated group compared with the group that received NaF treatment (Reddy *et al.*, 2009). The SOD, CAT and glutathione levels were decreased in NaF-treated group being selenium able to increase the expression the aforementioned enzymes (Reddy *et al.*, 2009). Glucose-6-phosphate dehydrogenase was decreased, and alkaline phosphatase and acid phosphatase increased in the brain of mice after the administration of NaF (Reddy *et al.*, 2009). All metabolic enzymes were significantly reversed after the administration of selenium to the NaF-treated group. Thus, the harmful effects induced by NaF on oxidative and metabolic enzymes of brain were reversible by selenium supplementation (Reddy *et al.*, 2009).

Fig. 1



Mechanisms of action induced by polyphenols and nonpolyphenols against fluoride toxicity. ROS, reactive oxygen species.

Conclusion

In this review, we have highlighted recent advancements in the effects of polyphenols and nonpolyphenols against the toxicity induced by fluoride either *in vitro* or *in vivo*. All published data show some evidence related to mitigation of the harmful effects induced by fluoride as a result of antioxidant action and inhibition of the apoptosis process (Fig. 1). Further studies should be carried out including on the use of other genotoxicity assays with different endpoints, such as mutation, chromosomal breakage as well as disruption of the genetic apparatus. Moreover, study of the role of fluoride in the interference of cellular signal pathways, gene-expression profiles closely related to the DNA repair system and epigenetic mechanisms, or to identify polyphenols or nonpolyphenols that can act as defluoridating agents is fundamental to elucidate the biological mechanisms of these bioactive compounds following systemic fluoride exposure. Certainly, new information will be added to that already established for regulatory purposes as a safe way to promote oral healthcare and prevent oral carcinogenesis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

Adedara IA, Abolaji AO, Idris UF, Olabiyi BF, Onibiyo EM, Ojuade TD, Farombi EO (2017). Neuroprotective influence of taurine on fluoride-induced biochemical and behavioral deficits in rats. *Chem Biol Interact* **261**:1–10.

Ameeramja J, Panneerselvam L, Govindarajan V, Jeyachandran S, Baskaralingam V, Perumal E (2016). Tamarind seed coat ameliorates fluoride induced cytotoxicity, oxidative stress, mitochondrial dysfunction and apoptosis in A549 cells. *J Hazard Mater* **301**:554–565.

Anantharaju PG, Gowda PC, Vimalambike MG, Madhunapantula SV (2016). An overview on the role of dietary phenolics for the treatment of cancers. *Nutr J* **15**:99.

Atmaca N, Yıldırım E, Güner B, Kabakçı R, Bilmen FS (2014). Effect of resveratrol on hematological and biochemical alterations in rats exposed to fluoride. *Biomed Res Int* **2014**:698628.

Bouasla A, Bouasla I, Boumendjel A, Abdennour C, El Feki A, Messarah M (2016). Prophylactic effects of pomegranate (Punica granatum) juice on sodium fluoride induced oxidative damage in liver and erythrocytes of rats. *Can J Physiol Pharmacol* **94**:709–718.

Bravo L (1998). Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. *Nutr Rev* **56**:317–333.

Campos-Pereira FD, Lopes-Aguiar L, Renosto FL, Nogueira GA, Costa EF, Barbieri Pulz R, *et al.* (2017). Genotoxic effect and rat hepatocyte death occurred after oxidative stress induction and antioxidant gene downregulation caused by long term fluoride exposure. *Chem Biol Interact* **264**:25–33.

Cao J, Chen J, Xie L, Wang J, Feng C, Song J (2015). Protective properties of sesamin against fluoride-induced oxidative stress and apoptosis in kidney of carp (Cyprinus carpio) via JNK signaling pathway. *Aquat Toxicol* **167**:180–190.

Cheynier V (2005). Polyphenols in foods are more complex than often thought. *Am J Clin Nutr* **81**:223s–229s.

Chiou SY, Sung JM, Huang PW, Lin SD (2017). Antioxidant, antidiabetic, and antihypertensive properties of echinacea purpurea flower extract and caffeic acid derivatives using in vitro models. *J Med Food* **20**:171–179.

Choubisa SL, Choubisa D (2016). Status of industrial fluoride pollution and its diverse adverse health effects in man and domestic animals in India. *Environ Sci Pollut Res Int* **23**:7244–7254.

Das J, Ghosh J, Manna P, Sil PC (2008). Taurine provides antioxidant defense against NaF-induced cytotoxicity in murine hepatocytes. *Pathophysiology* **15**:181–190.

Deng H, Kuang P, Cui H, Chen L, Luo Q, Fang J, *et al.* (2016). Sodium fluoride (NaF) induces the splenic apoptosis via endoplasmic reticulum (ER) stress pathway *in vivo* and *in vitro*. *Aging (Albany NY)* **8**:3552–3567.

Di Martino RM, Luppi B, Bisi A, Gobbi S, Rampa A, Abruzzo A, Belluti F (2017). Recent progress on curcumin-based therapeutics: a patent review (2012–2016). Part I: curcumin. *Expert Opin Ther Pat* **20**:1–12.

Goodarzi F, Mahvi AH, Hosseini M, Nedjat S, Nabizadeh Nodehi R, Kharazifard MJ, *et al.* (2016). The prevalence of dental fluorosis and exposure to fluoride in drinking water: a systematic review. *J Dent Res Dent Clin Dent Prospects* **10**:127–135.

Guney M, Oral B, Karahan N, Mungan T (2007). Protective effect of caffeic acid phenethyl ester (CAPE) on fluoride-induced oxidative stress and apoptosis in rat endometrium. *Environ Toxicol Pharmacol* **24**:86–91.

Hamza RZ, El-Shenawy NS, Ismail HA (2015). Protective effects of blackberry and quercetin on sodium fluoride-induced oxidative stress and histological changes in the hepatic, renal, testis and brain tissue of male rat. *J Basic Clin Physiol Pharmacol* **26**:237–251.

Harborne JB, Williams CA (1992). Advances in flavonoid research since 1992. *Phytochemistry* **55**:481–504.

Hassan HA, Yousef MI (2009). Mitigating effects of antioxidant properties of black berry juice on sodium fluoride induced hepatotoxicity and oxidative stress in rats. *Food Chem Toxicol* **47**:2332–2337.

Ho HH, Chang CS, Ho WC, Liao SY, Lin WL, Wang CJ (2013). Gallic acid inhibits gastric cancer cells metastasis and invasive growth via increased expression of RhoB, downregulation of AKT/small GTPase signals and inhibition of NF-κB activity. *Toxicol Appl Pharmacol* **266**:76–85.

Jetti R, Raghuveer CV, Mallikarjuna RC (2016). Protective effect of ascorbic acid and *Ginkgo biloba* against learning and memory deficits caused by fluoride. *Toxicol Ind Health* **32**:183–187.

Junrui P, Bingyun L, Yanhui G, Xu J, Darko GM, Dianjun S (2016). Relationship between fluoride exposure and osteoclast markers during RANKL-induced osteoclast differentiation. *Environ Toxicol Pharmacol* **46**:241–245.

Kanagaraj VV, Panneerselvam L, Govindarajan V, Ameeramja J, Perumal E (2015). Caffeic acid, a phyto polyphenol mitigates fluoride induced hepatotoxicity in rats: a possible mechanism. *Biofactors* **41**:90–100.

Li W, Jiang B, Cao X, Xie Y, Huang T (2017). Protective effect of lycopene on fluoride-induced ameloblasts apoptosis and dental fluorosis through oxidative stress-mediated caspase pathways. *Chem Biol Interact* **261**:27–34.

Mansour HH, Tawfik SS (2012). Efficacy of lycopene against fluoride toxicity in rats. *Pharm Biol* **50**:707–711.

Miltonprabu S, Thangapandiyan S (2015). Epigallocatechin gallate potentially attenuates fluoride induced oxidative stress mediated cardiotoxicity and dyslipidemia in rats. *J Trace Elem Med Biol* **29**:321–335.

Nabavi SF, Nabavi SM, Latifi AM, Mirzaei M, Habtemariam S, Moghaddam AH (2012a). Mitigating role of quercetin against sodium fluoride- induced oxidative stress in the rat brain. *Pharm Biol* **50**:1380–1383.

Nabavi SF, Nabavi SM, Mirzaei M, Moghaddam AH (2012b). Protective effect of quercetin against sodium fluoride induced oxidative stress in rat's heart. *Food Funct* **3**:437–441.

Nabavi SM, Nabavi SF, Moghaddam AH, Setzer WN, Mirzaei M (2012c). Effect of silymarin on sodium fluoride-induced toxicity and oxidative stress in rat cardiac tissues. *An Acad Bras Cienc* **84**:1121–1126.

Nabavi SF, Nabavi SM, Abolhasani F, Moghaddam AH, Eslami S (2012d). Cytoprotective effects of curcumin on sodium fluoride-induced intoxication in rat erythrocytes. *Bull Environ Contam Toxicol* **88**:486–490.

Nabavi SF, Moghaddam AH, Eslami S, Nabavi SM (2012e). Protective effects of curcumin against sodium fluoride-induced toxicity in rat kidneys. *Biol Trace Elem Res* **145**:369–374.

Nabavi SF, Habtemariam S, Sureda A, Hajizadeh Moghaddam A, Daglia M, Nabavi SM (2013a). In vivo protective effects of gallic acid isolated from Peltiphyllum peltatum against sodium fluoride-induced oxidative stress in rat erythrocytes. *Arh Hig Rada Toksikol* **64**:553–559.

Nabavi SM, Habtemariam S, Nabavi SF, Moghaddam AH, Latifi AM (2013b). Prophylactic effects of methyl-3-O-methyl gallate against sodium fluoride-induced oxidative stress in erythrocytes in vivo. *J Pharm Pharmacol* **65**:868–873.

Niu Q, Mu L, Li S, Xu S, Ma R, Guo S (2016). Proanthocyanidin protects human embryo hepatocytes from fluoride-induced oxidative stress by regulating iron metabolism. *Biol Trace Elem Res* **169**:174–179.

Pal S, Sarkar C (2014). Protective effect of resveratrol on fluoride induced alteration in protein and nucleic acid metabolism, DNA damage and biogenic amines in rat brain. *Environ Toxicol Pharmacol* **38**:684–699.

Petersen PE, Kwan K, Zhu L, Zhang BX, Blan JY (2008). Effective use of fluorides in the People's Republic of China – a model for WHO Mega Country initiatives. *Comm Dental Health* **25** (**Suppl 1**):257–267.

Qadir MI, Naqvi ST, Muhammad SA (2016). Curcumin: a polyphenol with molecular targets for cancer control. *Asian Pac J Cancer Prev* **17**:2735–2739.

Reddy KP, Sailaja G, Krishnaiah C (2009). Protective effects of selenium on fluoride induced alterations in certain enzymes in brain of mice. *J Environ Biol* **30** (**Suppl**):859–864.

Ribeiro DA, Hirota L, Cestari TM, Ceolin DS, Taga R, Assis GF (2006). Ultrastructural morphometric analysis of ameloblasts exposed to fluoride during tooth development. *J Mol Histol* **37**:361–367.

Sarkar C, Pal S, Das N, Dinda B (2014). Ameliorative effects of oleanolic acid on fluoride induced metabolic and oxidative dysfunctions in rat brain: experimental and biochemical studies. *Food Chem Toxicol* **66**:224–236.

Shanmugam T, Selvaraj M, Poomalai S (2016). Epigallocatechin gallate potentially abrogates fluoride induced lung oxidative stress, inflammation via Nrf2/Keap1 signaling pathway in rats: an in-vivo and in-silico study. *Int Immunopharmacol* **39**:128–139.

Sharma C, Suhalka P, Sukhwal P, Jaiswal N, Bhatnagar M (2014). Curcumin attenuates neurotoxicity induced by fluoride: an in vivo evidence. *Pharmacogn Mag* **10**:61–65.

Shlisky J, Bloom DE, Beaudreault AR, Tucker KL, Keller HH, Freund-Levi Y, *et al.* (2017). Nutritional considerations for healthy aging and reduction in age-related chronic disease. *Adv Nutr* **8**:17–26.

Suzuki M, Bandoski C, Bartlett JD (2015). Fluoride induces oxidative damage and SIRT1/autophagy through ROS-mediated JNK signaling. *Free Radic Biol Med* **89**:369–378.

Swenberg JA, Bogdanffy MS, Ham A, Holt S, Kim A, Morinello EJ, *et al.* (1999). Formation and repair of DNA adducts in vinyl chloride- and vinyl fluoride-induced carcinogenesis. *IARC Sci Publ* **150**:29–43.

Thangapandiyan S, Miltonprabu S (2013). Epigallocatechin gallate effectively ameliorates fluoride-induced oxidative stress and DNA damage in the liver of rats. *Can J Physiol Pharmacol* **91**:528–537.

Tiwari H, Rao MV (2010). Curcumin supplementation protects from genotoxic effects of arsenic and fluoride. *Food Chem Toxicol* **48**:1234–1238.

Tsao R (2010). Chemistry and biochemistry of dietary polyphenols. *Nutrients* **12**:1231–1246.

Umarani V, Muvvala S, Ramesh A, Lakshmi BV, Sravanthi N (2015). Rutin potentially attenuates fluoride-induced oxidative stress-mediated cardiotoxicity, blood toxicity and dyslipidemia in rats. *Toxicol Mech Methods* **25**:143–149.

Vasant RA, Narasimhacharya AV (2012). Ameliorative effect of tamarind leaf on fluoride-induced metabolic alterations. *Environ Health Prev Med* **17**: 484–493.

Zhang C, Ren C, Chen H, Geng R, Fan H, Zhao H, Guo K, Geng D (2013). The analog of *Ginkgo biloba* extract 761 is a protective factor of cognitive impairment induced by chronic fluorosis. *Biol Trace Elem Res* **153**:229–236.

Zhang Z, Zhou B, Wang H, Wang F, Song Y, Liu S, Xi S (2014). Maize purple plant pigment protects against fluoride-induced oxidative damage of liver and kidney in rats. *Int J Environ Res Public Health* **11**:1020–1033.