Concise Review

Potential Oral Health Benefits of Ginseng and Its Extracts

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ARTICLE INFO

Article history:
Received 26 November 2022
Received in revised form
23 February 2023
Accepted 26 February 2023
Available online 21 April 2023

Key words:
Ginseng
Dental caries
Periodontitis
Oral cancer
Oral mucosal disease

ABSTRACT

This review discusses the effects of ginseng and its extracts in the treatment of dental caries, periodontal diseases, endodontic diseases, oral cancers, oral mucosal diseases, and some other dental associations. In the meantime, bioavailability and safety application of ginseng products are discussed. All of the articles reviewed were from PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Wanfang Data, and VIP Chinese Science and Technology Periodicals Full-Text Database through November 2022, including full-text English or non-English publications. Ginseng and its extracts were shown to have beneficial effects on oral diseases, and further studies are needed to understand the mechanisms and confirm the effects in humans.

Introduction

Ginseng and its extracts have anti-inflammatory, antioxidative, anticancer, bacteriostatic, antiaging, antifatigue, antidiabetic, antistress, and antidepressant properties.[1] Thus, ginseng has shown curative effects on many diseases. The constituents of ginseng include carbohydrates, alkaloids, amino acids, polypeptides, vitamins, trace elements, and enzymes. Amongst these, the major active ingredients of ginseng are ginsenosides. Ginsenosides are a class of steroid compounds, also known as triterpenoid saponins, which are normally extracted from roots.[2] Ginsenosides differ primarily in their types, numbers, and positions of sugars, C-20 side chains, and stereoisomerism. Generally speaking, ginsenosides can be divided into 3 categories. The first category is protopanaxadiol (PPD), which includes ginsenosides Ra1, Ra2, Ra3, Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, Rs1, and Rs2 and notoginsenoside R4. The second category is protopanaxatriol (PPT), including ginsenosides Re, Rf, Rg1, Rg2, and Rh1 and notoginsenoside R1. The third category is the oleanolic acid type (OA), including ginsenoside Ro. PPD and PPT account for the majority of ginsenosides. The difference between the 2 groups is the position of sugar moieties. PPD group sugar molecules are bound to C-3 and/or C-20 of sapogenin to form oxyglycoside, whereas PPT group sugar molecules are bound to C-6 and/or C-20 of sapogenin to generate oxyglycoside (Figure).

In recent years, several studies have evaluated the benefits of ginseng and its extracts in prevention and treatment of oral health conditions and symptoms. Therefore, in this review, we discussed the properties of ginseng and its extracts and highlighted their potential applications in oral health (Table).

Methods

The databases were including PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP Chinese Science and Technology Periodicals Full-Text Database through November 2022. The articles were searched by using the keywords ginsenoside, ginseng, oral diseases, dental diseases, caries, dental caries, periodontal diseases, periodontitis, pulpitis,

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https://doi.org/10.1016/j.identj.2023.02.004

Ginsenoside	R1	R2	R3
protopanaxadiol (PPD)			
Rb1	glu-glu	-H	glu-glu
protopanaxatriols (PPT)			
Rg1	-H	O-glu	glu-glu

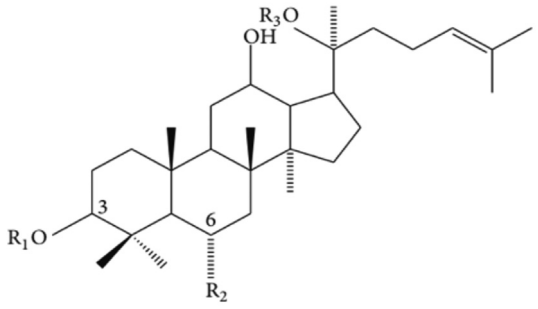

Fig – Structure of ginsenosides Rb1 and Rg1.

endodontic disease, oral cancer, oral mucosal disease, oral implantology, and halitosis. For example, a search strategy in PubMed was as follows: ((ginsenoside) OR (ginseng)) AND (caries). The selected literature published in English and non-English. Two authors (YP and XC) independently screened titles and abstracts to remove papers that were duplicates or completely off-topic. The 41 remaining articles were reviewed carefully and their findings were critically analysed.

Results and discussion

Dental caries

Cariogenic microbes are major factors leading to the onset and development of dental caries, including *Streptococcus mutans*, *Streptococcus sobrinus*, and *Streptococcus sanguis*. Moreover, studies have found that *Candida albicans* exists in dental plaque biofilms of children's dental cavities[3–5] and promote the growth of *Streptococcus mutans* due to the chemically related effect between them.[6] Therefore, reducing cariogenic microbes, limiting acid synthesis, and controlling cariogenic biofilm formation have been proven to be effective strategies for preventing and treating dental caries.[7]

Cao et al[8] used ginsenoside Rh2 to treat multiple or single *Streptococcus mutans*, *Streptococcus sobrinus*, and *Streptococcus sanguinis* biofilms in vitro. It had been shown that Rh2 could significantly reduce biomass by inhibiting bacterial growth and exopolysaccharide synthesis from the beginning of biofilm formation without toxicity. Moreover, the rat caries model showed that the caries scoring in the Rh2-treated group was lower than that in the control group. This may be related to Rh2 regulating biofilm metabolism through phosphotransferase system and the butyrate metabolism pathway. Mannose-specific IIC/D components as well as acetaldehyde/alcohol dehydrogenase might be the key targets of Rh2 achieving its antibiofilm effect. The work indicated that Rh2 could inhibit the formation of cariogenic biofilms in vitro and had caries protective effect in rat model.[9] Other researches demonstrated the antibacterial activity of ginseng extract (mainly ginsenoside Rb2, Rd, Re, and ginseng polysaccharide) against *Candida albicans* due to their ability to disrupt cell membrane structures.[10–12]

Recent studies have revealed that ginseng extracts had multiple effects on the immune system, including stimulation of lymphocyte proliferation, macrophage cytokine production, and improvement of macrophage and polymorphonuclear leukocyte phagocytic activity. Their adjuvant effects may be applied in the activation of natural and specific immune responses.[13–18] An in vivo study demonstrated that ginsenoside Re, as an adjuvant for the anticaries subunit vaccine rPAc, increased specific antibodies in serum and saliva of the anticaries vaccine.[19] It was also speculated that the mechanism might involve the modulation of T-bet/GATA-3 gene expression, which resulted in the increase of interleukin (IL)-4 and interferon-γ expression in lymphocytes.

Periodontal disease

Periodontal diseases, including gingivitis and periodontitis, involve inflammation of the periodontal tissues. Gingivitis affects only the gingival soft tissues, whilst periodontitis can result in destruction of periodontal supporting tissues, such as the gingiva, periodontium, and alveolar bone. Periodontitis can be caused by 2 main factors: (1) pathogenic microorganisms that accumulate and colonise in the subgingival area and produce toxins and proteases to destroy normal periodontal tissues (eg, *P gingivalis* can accumulate in periodontal pockets and secrete virulence factors like gingipains, which will do harm to periodontal cells and cause inflammation)[20] or (2) host immune response to the pathogens (in the serum or gingival crevicular fluid of patients with periodontitis, high-titer specific antibodies to periodontal pathogens can often be detected, and this antibody decreases after periodontal treatment).[21] Periodontal treatment should focus on anti-inflammatory and promotion of periodontal tissue regeneration.

Kim et al[22,23] found that ginsenosides Re, Ra8, Rf, and Panax ginseng fruit extract (PGFE) promoted osteodifferentiation of human periodontal ligament stem cells (HPDLCs) by promoting nuclear transcription factor (Nrf2) translocation and producing heme oxygenase 1 (HO-1). They could also inhibit loss of alveolar bone and expression of pro-inflammatory factors (tumour necrosis factor-alpha [TNF-α] and IL-6). Furthermore, it could promote the expression of osteoblast-specific genes such as alkaline phosphatase (ALP), Osteopontin (OPN), and Runt-related transcription factor 2 (RUNX2). Wang et al[24] also reported that ginsenoside Rd could reduce the inhibitory effect of oxidative stress on HPDLC osteogenesis, which provided a theoretical basis for the use of Rd in the treatment of diabetic periodontitis. Liu et al[25] revealed that ginsenoside Rg1 could regulate the proliferation and migration of HPDLC under nicotine stress through the Protein Kinase B (Akt)/endothelial nitric oxide synthase (eNOS) signaling pathway. Similarly, Sun et al[26] reported that ginsenoside Rb3 ameliorated *P gingivalis* lipopolysaccharide (LPS)-induced inflammation by inhibiting the mitogen-activated

Table – Application of ginseng and its extracts in oral health.

Oral disease/ treatment/symptom	Active compound	Experimental model	Treatment effects	Mechanism	Reference
Dental caries	Ginsenoside Rh2, Re, Rb2, Rd, and ginseng polysaccharide	*Streptococcus mutans*, *Streptococcus sobrinus*, and *Streptococcus sanguinis* or *Candida albicans* in culture; caries rat model; anticaries vaccine mouse model; healthy people use mouthwashes	Inhibit biofilm formation of cariogenic bacteria; bacterial death; decrease in caries development; increase in specific antibodies	Regulate phosphotransferase system, butyrate metabolism pathway, mannose-specific IIC/D components, acetaldehyde/alcohol dehydrogenase; disrupt cell membrane structures; modulate T-bet/GATA-3 gene expression	8-13,20
Periodontal disease	Ginsenoside Re, Ra8, Rf, Rb3, Rg1, Rd, and PGFE	LPS-stimulated HPDLC in culture; periodontitis rat model; generalised chronic periodontitis patients use mouthwashes	Inhibit loss of alveolar bone; promotion of periodontal tissue regeneration; decrease in plaque index, gingival index, and bleeding index	Nrf2 translocation; produce HO-1; inhibit proinflammatory factor production; Akt/eNOS and MAPK/AKT/NF-κB pathway	23-35
Endodontic disease	Ginsenoside Rg1 and NR1	Transwell dentin disc tube model; injection gel mouse model; TEGDMA-induced mitochondrial apoptosis in dentin precursor cells; human dental pulp stem cell culture	High dentin permeability; induction of dentin formation; protection of pulp; proliferation and differentiation of human pulp stem cell	Inhibit Akt/Nrf2, cell cycle, MAPK, TGF pathway; increase the expression of DSPP, ALP, OCN, BMP-2, DMP1, and FGF2	37-42
Oral cancer	Ginsenoside M1, Rh2, Rb3, and ginseng fructose polysaccharide	Oral cancer cell culture; tumour mouse model; xenograft nude mice model	Inhibit the growth, invasion, and migration of oral cancer cell; reduce tumour growth; protect kidney from cisplatin toxicity	Increase the expression of Bak, Bad, and p53; induce apoptotic DNA fragmentation, G1, and G2/M phase block; activate Caspase-3; inhibit MMP-2; decrease VEGF expression; Src/Raf/ERK pathway; remove ROS; regulate EMT-related proteins; regulate TGF-β pathway-mitochondrial apoptosis	43-47
Oral mucosal disease					
Oral mucositis	Ginsenoside Rb1 and ginseng polysaccharide	5-FU-induced oral mucositis hamster model; clinical trial	Reduce ulcer and abscess formation; Reduce injury grading	Inhibit production of proinflammatory factors; reduce myeloperoxidase activity	48,49
Oral leukoplakia	Ginsenoside Rh2	Buccal leukoplakia dynamic rat model	Inhibit oral leukoplakia carcinogenesis	Unknown	50
Oral implantology	Ginsenoside Rb1, Rg1 and NR1	Human alveolar bone osteoblasts in culture; titanium nanotube loaded with red ginseng extract microimplants implant in mice	Promote alveolar bone regeneration; periimplant bone formation	Inhibit NF-κB pathway; activate Wnt/β-linked protein pathway; increase BMP-2, BMP-7, and collagen	53-57
Halitosis	Ginsenoside Rg2, Rg3, Rg6, F4, Rg5, Rk1, and red ginseng extracts	*Fusobacterium nucleatum*, *Clostridium perfringens*, and *Porphyromonas gingivalis* in culture; clinical trial	Bacterial inhibition; resolution of halitosis	Reduce the expressions of cystathionine γ-lyase and IL-6, IL-8, and IL-1β mRNA	59,60

Akt, protein Kinase B; ALP, alkaline phosphatase; BMP, bone morphogenetic protein; DMP, dentin matrix protein; DSPP, dentin sialophosphoprotein; EMT, epithelial mesenchymal transition; FGF, fibroblast growth factor; HPDLC, human periodontal ligament stem cells; HO, heme oxygenase; IL, interleukin; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; OCN, osteocalcin; PGFE, Panax ginseng fruit extract; ROS, reactive oxygen species; TEGDMA, triethylene glycol dimethacrylate; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

protein kinase (MAPK)/AKT/nuclear factor (NF)-κB signaling pathway.

Based on the rat model of periodontitis, researchers found that ginseng and its extracts also had obvious protective effects on periodontal tissues through inhibiting bone resorption, decreasing osteoclastogenesis, and supporting periodontal regeneration.[26–31] Yang et al also found that ginsenoside Rg1 had a protective effect on diabetic periodontitis rats.[32,33]

A clinical trial was conducted on 30 patients with generalised chronic periodontitis. Researchers found that the application of red ginseng mouthwash and chlorhexidine had the same efficacy whilst was more effective than the control group (placebo).[34]

Endodontic disease

Dental pulp and dentin are closely related in embryogenesis and have interconnected effects in response to external stimuli, which can be regarded as a biological whole, called the pulpodentinal complex.[35] When enamel and cementum are lost, the exposed dentinal tubules become the conduits between dental pulp and the external oral environment. Pulp capping is a method of preserving viable pulp, which is of great significance to the health of teeth. Ideally, a pulp capping drug should promote the regeneration of dental pulp tissue, be highly biocompatible, possess antibacterial and anti-inflammatory effects, exhibit strong permeability, and provide stable efficacy. Scholars have also done some research on the application of ginsenosides in pulp capping drugs.

Lin et al[36] established a transwell dentin disc tube model in vitro and compared the permeability of 7 anti-inflammatory drugs to dentin. There were 2 corticosteroids (betamethasone sodium phosphate and hydrocortisone sodium succinate), 3 nonsteroidal anti-inflammatory drugs (piroxicam, lysine acid sodium acetylsalicylate, and diclofenac sodium), and 2 natural extracts (ginsenoside Rg1 and hinokitiol) included in the study. The results showed that ginsenoside Rg1 possessed the highest degree of dentin permeability amongst these anti-inflammatory drugs, providing a basis for the treatment of dentin hypersensitivity, pulp inflammation, pulp necrosis, or apical abscess. In another study, ginsenoside Rg1 was found to have the ability to promote the proliferation of human dental pulp cells.[37] Wang et al[38] developed an injectable colloidal gel using methacrylic acid −functionalised gelatin loaded with notoginsenoside R1 (NR1) and conducted in vitro and in vivo experiments in mice. In vitro experiments revealed that the hydrogel could boost the expression of dentin markers such as ALP (a marker of early dentin differentiation) and osteocalcin (OCN, a marker of late dentin differentiation) as well as extracellular matrix mineralisation, resulting in a significant increase in the odontogenic differentiation of mouse dental papilla cells. In vivo study in mice demonstrated the effectiveness of the gel in dentin formation and found that the relative volume of calcification formation was increased by approximately 175-fold. Based on the above results, the hydrogel appeared to be a very effective pulp capping material in stimulating dentin formation. Moreover, researchers found that NR1 had a significant effect on the mitochondrial apoptosis of dentin precursor cells induced by resin monomers such as triethylene glycol dimethacrylate (TEGDMA). The mechanism lay in the inhibition of the Akt/Nrf2 pathway, which significantly reduced cellular antioxidant properties and aggravated mitochondrial oxidative damage in TEGDMA-treated cells. Applications of NR1 might offer a promising strategy to prevent resin monomer-related pulp damage.[39]

Besides the functions mentioned above, ginseng and its extracts were also effective treatments for dental pulp regeneration. Researchers found that ginsenoside Rg1 could enhance the proliferation of human dental pulp stem cells (HDPSCs) and the differentiation of odontoblasts.[40] Ginsenoside Rg1 induced gene expression of dentin sialophosphoprotein, ALP, OCN, bone morphogenetic protein-2 (BMP-2), dentin matrix protein 1 (DMP1), and fibroblast growth factor 2. Several pathways were identified with statistical significance, including the cell cycle pathway, MAPK signaling pathway, and transforming growth factor (TGF) signaling pathway. In this case, ginsenoside Rg1 was a potential candidate for endodontic biotherapy, restorative dentin formation, and dental tissue engineering.

Oral cancer

Oral squamous cell carcinoma (OSCC) is the most common histologic type of oral cancer. It has been shown that ginseng and its extracts may be useful in the prevention and treatment of OSCC because of their potent antitumour properties, which are capable of modulating various signaling pathways in malignant tumours.

Researchers investigated that ginsenoside M1 caused an increase in Bak, Bad, and p53 expression and induced apoptotic DNA fragmentation.[41] It also caused PI/Annexin V double positive staining and caspase 3-9 activation, which led to apoptosis of oral cancer cell. Additionally, ginsenoside M1 inhibited cancer cell migration and colony formation, whilst decreasing the expression of vimentin and metastasis. Mice injected orally or subcutaneously with ginsenoside M1 showed significant tumour growth reduction. Another in vitro experiment[42] found that ginseng fructose polysaccharide could induce a cascade reaction by inducing G2/M phase arrest and activating Caspase-3, thereby it induced apoptosis and inhibited the proliferation of human tongue squamous cells. There are more studies on the anticancer effect of ginsenoside Rh2. Zhang et al[43] found that ginsenoside Rh2 inhibited matrix metalloproteinase-2 (MMP-2) by blocking the invasion and migration of oral cancer cells. Ginsenoside Rh2 could reduce the expression of vascular endothelial growth factor (VEGF), thereby suppressing tumour angiogenesis. Furthermore, it could eliminate reactive oxygen species (ROS) that induced VEGF secretion. According to an in vitro study,[44] the anticancer effects of ginsenoside Rh2 were mediated via its ability to induce apoptosis and arrest in the G0/G1 phase of the cell cycle. It could also regulate the migration and invasion of EMT (epithelial-mesenchymal-transition)-related proteins and inhibit the Src/Raf/ERK signaling pathway in vitro. Further studies are required to determine its effectiveness in treating oral cancer.

In addition to the direct inhibition of oral cancer, ginsenosides have a protective effect in chemotherapy. In xenograft nude mice model bearing oral carcinoma cells, the protective effects of ginsenoside Rb3 on cisplatin-evoked kidney toxicity through TGF-β pathway-mitochondrial apoptosis[45] had been found.

Oral mucosal disease

Patients with cancer may also have oral mucositis, a complication caused by chemotherapy and radiotherapy. In the hamster model, chitosan-sodium alginate films containing ginsenoside Rb1 not only promoted the healing of 5-fluorouracil (5-FU)-induced injury but also decreased the ulcer area, activity of myeloperoxidase, and infiltration of inflammatory cells.[46] It seemed that topical application of ginsenoside Rb1 to mucositis had a healing effect. Compared with Xipayi mouth rinse therapy, ginseng polysaccharide injection combined therapy could decrease the total score of oropharyngeal pain and the grade of the oral mucosa of patients with radiation-induced oral mucositis.[47]

Oral leukoplakia is a relatively common oral mucosal disease and is a recognised precancerous lesion. Researchers[48] set up a dynamic model of buccal leukoplakia in SD rats using 30 cases divided into saline and ginsenoside Rh2, respectively. The histologic distribution of cancer in rats treated with Rh2 was significantly lighter than in their counterparts, suggesting that Rh2 inhibited oral leukoplakia carcinogenesis.

Oral implantology

Modern oral implantology is based on osseointegration theory.[49] Two factors influence the stabilisation of the implant during osseointegration after dental implantation: (1) the surface characteristics of the implant which compromise the attachment of proteins to the implant and the subsequent cellular processes associated with osseointegration and (2) bone formation stimuli.[50]

Ginseng and its extracts have been shown to promote osteoblast differentiation and alveolar bone regeneration in several studies.[51–54] According to in vitro study,[53] NR1 promoted alveolar bone regeneration by inhibiting the NF-κB pathway and activating the Wnt/β-linked protein pathway in the TNF-α-induced inflammatory microenvironment. In terms of specific studies, Kang et al[55] investigated whether implantation of titanium nanotubes (N-Ti) loaded with Korean red ginseng extract (KRGE, containing mainly ginsenosides Rb1 and Rg1) micro-implants affected osteogenesis and osseointegration. Compared to pure titanium without KRGE loading, KRGE-coated implant significantly increased the proliferation and differentiation of mouse cranial osteogenic precursor cells in vitro. Moreover, in vivo experiments showed that new bone formation and bone density were significantly higher in the peri-implant tissues of edentulous rat jaws. Moreover, collagen, high levels of BMP-2 and BMP-7 were detected in peri-implant tissues. The results indicated that KRGE-induced peri-implant osteogenesis and osseointegration in micro-implants might contribute to its clinical application.

Halitosis

Halitosis, or oral malodour, refers to a smell coming from the mouth or breath that is unpleasant. Volatile sulfur compounds (VSC, mainly hydrogen sulfide, methyl mercaptan, and dimethyl sulfide) are the cause of this condition. The main bacteria responsible for producing VSC are *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Helicobacter pylori*, and others.[56] Ginsenosides control halitosis mainly via 2 mechanisms: (1) controlling the growth of VSC-producing microorganisms and (2) inhibiting the production of VSC by supressing the expression of VSC-associated enzymes or other molecules.[57]

Less polar ginsenoside-enriched fraction (Rg2, Rg3, Rg6, F4, Rg5, and Rk1) from heat transformation could effectively inhibit the growth of periodontal pathogen *Fusobacterium nucleatum*, *Clostridium perfringens*, and *Porphyromonas gingivalis in vitro*.[58] Hence, the extracts could effectively treat halitosis resulting from these anaerobic bacteria. In their analysis, ginsenoside Rg5 was found to have the highest antibacterial activity with the lowest concentrations of both minimum inhibitory concentration and minimum bactericidal concentration. Korea red ginseng was effective in relieving oral malodour in patients with *H pylori* because red ginseng extracts significantly reduced *H pylori* or Sodium hydrosulfide (NaHS)-induced ystathionine γ-lyase expression as well as attenuated levels of IL-6, IL-8, and IL-1β mRNA.[59]

Challenges of ginseng and its extracts

Even though ginseng had potential applications in oral diseases treatment, its unfavourable physicochemical and pharmaceutical properties were its main drawback. Oxidation and dehydrogenation reactions, environmental conditions, and processing and handling of plant materials may cause degradation and ultimately alter their properties. To overcome this problem, studies had been conducted to load ginseng and its extracts by biopolymers carriers such as chitosan, micro-nano hydroxyapatite, and silk fibronectin to repair bone defects[51,52] and hydrogels.[28,29] These findings have paved the way for the practical application of ginseng and its extracts in the future.

Furthermore, we have to be aware of the possible safety issues associated with ginseng and its extracts. These include bleeding and drug reactions.[60] In light of ginseng's antiplatelet and anticoagulant properties,[61-63] caution should be exercised when taking supplements with such medications. It is recommended to stop taking ginseng 24 hours before surgery based on its pharmacokinetics.[64] Calabrese et al reviewed the hormetic dose-dependance of ginsenoside Rg1 on HPDLSCs and HDPSCs. Rg1 had a negative effect at high doses and a beneficial effect at low doses. Consequently, we should pay attention to the dose issue in the application of ginseng and its extracts.[65,66]

Conclusions

Evidence suggested that ginseng's antibacterial, anti-inflammatory, anticancer, and osteogenic properties have beneficial effects on oral health. However, most of the studies have been conducted in cell culture and animals. Therefore, further studies about the exact mechanisms and clinical trails confirming the effects are necessary in the future.

Author contributions

YP conceived and designed the work, conducted the literature research, drafted the manuscript, and approved the final version of the manuscript. WP revised the manuscript and approved the final version. XC conducted the literature research, revised the manuscript, and approved the final version. CL conceived and designed the work, revised the manuscript, approved the final version approval, and contributed to funding acquisition.

Conflict of interest

None disclosed.

Funding

This work was supported by a grant from the National Natural Science Foundation of China (grant number 81201260).

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