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Cancer preventive and neuroprotective potentials of red hulls, kernels and oleo-gum resins from Pistachio

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Abstract

This research was performed to assess cancer prevention and neuroprotective capacities of different parts of Pistachio (*Pistachio vera* L.). Red hulls, kernels and oleo-gum resins of Pistachio were extracted with methanol-MeOH and distilled water-dH_2O, and subjected to *in vitro* biological assays varying from 100 to 1000 µg mL^{-1} concentrations. Their anticancer activities were evaluated against A549, MCF-7, and HeLa human cancer cells. Neuroprotective activities of the extracts were tested through enzyme inhibition on AChE, BChE, and TYR, which are closely related to pathogenesis of neurobiological disorders, particularly Alzheimer's and Parkinson's diseases. Due to cancer and neurodegenerative diseases are associated with oxidative damage, the extracts were analyzed for their antioxidant activities. With respect to free radical scavenging activities of the extracts, red hull extracts were found as the most potent ones both DPPH (67.95±1.13 to 80.55±0.12%) and ABTS (86.92±0.10 to 92.04±1.06%) radicals. The highest anticancer activity were determined in MeOH and dH_2O extracts obtained from oleo-gum resin against HeLa cells (IC_{50} = 18.50±0.85 and 28.97±0.08 µg mL^{-1}, $p< 0.01$, respectively), whilst dH_2O-kernel extract was found to have the weakest anticancer activity towards A549 cells (IC_{50} = 268.66±1.02 µg mL^{-1}, $p< 0.01$). Neuroprotective potentials on AChE and BChE enzymes were resulted in the superiority of dH_2O-red hull extract was exerted the highest inhibition on AChE and BChE enzymes with 81.50±0.08 and 62.96±1.01% inhibition, respectively. However, dH_2O extract from oleo-gum resin showed the highest inhibitory effect on TYR enzyme (58.16±0.18% inhibition). *P. vera* is of valuable nutritional source for human diet. Other than kernel parts used as food, waste parts like red hulls and oleo-gum resins have been proven as a potential pharmacological source. Consequently, this study reveals that non-food parts of Pistachio could be valuable source for pharmaceutical industry.

Keywords: Pistachio, Cancer Prevention, Neuroprotective, Antioxidant, Enzyme Inhibition

Introduction

Cancer and neurological diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), prion and motor neuron diseases etc. are of the most common diseases and disorders that cause a growing health problem worldwide. According to World Health Statistics reports, these diseases and disorders affect millions of people globally, and their incidence rates are expected to continue to increase rapidly for the following years. Currently, no effective therapy has still been revealed to fight cancer and neurodegenerative diseases, and thus dietary plants and their natural bioactive compounds offer extremely great opportunities for development effective treatment strategies (Newman and Cragg, 2016; Gezici, 2019a; Gezici and Sekeroglu, 2019a; WHO, 2019). Dietary medicinal plants (fruits, vegetables, spices, cereals, and edible tubers/roots) containing natural bioactive compounds such as phenolic acids, flavonoids, tannins, stilbenes, curcuminoids, resveratrol, lycopene,

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carotenoids, quercetin, catechin, naringenin, organosulfur, curcumin, genistein, isothiocyanates, capsaicin, gingerol, anthocyanins, coumarins, lignans, quinones, and others have been demonstrated to possess valuable health benefits beside basic nutrition (Das and Gezici, 2018; Guizani et al., 2018; Roy et al., 2018,).

Recently, dietary medicinal plants have been gained a great interest to reduce Reactive Oxygen Species (ROS) including hydroxyl radical (OH), hydrogen peroxide (H_2O_2) and superoxide ion (O_2) formation, occurring naturally in the human body. In living organisms, preventing the side effects of ROS is one of the most effective management strategy for oxidative-stress related diseases including cancer, cardiovascular disease, chronic kidney diseases, aging, diabetes, rheumatoid arthritis atherosclerosis, and neurodegenerative diseases (Reddy et al., 2003; Schieber and Chandel, 2014; Farzaei et al., 2018).

In the last few decades, natural antioxidants obtaining by dietary intake have a widespread interest instead of synthetic ones amongst the people. Previous studies have determined that a numerous natural herbal products and formulations obtained from dietary medicinal plants as natural antioxidant agents with powerful antioxidant capacities for reducing free radicals, metal chelators and singlet oxygen species (Reddy et al., 2003; Tabatabaei-Malazy et al., 2013; Guizani et al., 2018; Gezici and Sekeroglu, 2019b).

Among the dietary medicinal plants, Pistachio (*Pistacia vera* L.), belonging to the Anacardiaceae family, is native to Asia and distributed throughout the Mediterranean region (Bozorg et al., 2013). This plant has recently been ranked rich sources of antioxidants, and investigated for various pharmacological activities such as anti-inflammatory, antioxidant and antimicrobial activities, because of its wide range of secondary metabolites such as α-pinene, limonene, terpinolene, β-ocimene, camphene, resveratrol, carvacrol, abietadiene, gallic acid, catechin, eriodictyol, naringenin, genistein, apigenin, kaempferol, luteolin, cyanidin-3-galactoside (Rajaei et al., 2010; Bozorg et al., 2013).

Recent studies showed that Pistachio with whole parts including fruit, leave, gum, hull, oil, and seed possess potential usage for pharmacological purposes in traditional medicine, due to their comprehensive biological properties. In addition to their pharmacological usage, fruits of Pistachio have been commonly consumed as snack food and food additive (Rajaei et al., 2010; Fathalizadeh et al., 2015; Seifaddinipour et al., 2018).

By now, anticancer, antiproliferative, anticholinesterase, antityrosinase, antioxidant, and other biological activities of numerous medicinal and aromatic plants (MAPs) and secondary metabolites isolated from MAPs were analysed in our laboratory (Akgunlu et al., 2016; Sekeroglu et al., 2017; Gezici et al., 2017; Belkhodja et al., 2017; Karik et al., 2018; Gundogdu et al., 2018; Senol et al., 2018; Gezici, 2018; Sekeroglu et al., 2018; Das et al., 2019; Shida et al., 2019; Gezici and Sekeroglu, 2019a; Gezici and Sekeroglu, 2019b; Gezici, 2019a; Gezici 2019b; Sekeroglu and Gezici, 2019, Sekeroglu et al., 2019 *in press*). Take into consideration our ongoing projects, evaluation cancer protective potentials against human cancer cells, investigating neuroprotective activities through enzyme inhibitions on acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and TYR (tyrosinase) enzymes, along with determination of antioxidant capacities of extracts obtained from red hulls, kernels and oleo-gum resins of Pistachio (*P. vera* L.) are the main objectives of the presented research.

Materials and Methods

Collection of Plant Material

Red hulls, kernels, and oleo-gum resins of Pistachio (*Pistachio vera* L.) used herein were collected from Gaziantep province of Turkey during the months of August - September 2018. The red hulls were separated from the kernels, and the hulls and kernels were dried in the laboratory conditions. The herbarium voucher of plant samples was kept at the Department of Biology, Kilis 7 Aralık University, Turkey.

Extraction of Plant Parts

P. vera L. parts including red hulls (PVRH) and kernels (PVK) were dried under the shade at laboratory conditions. The oleo-gum resins of pistachio (PVOR) was directly subjected to extraction after collection from the plant stem. Each plant part (50g) was powdered individually, and extracted with methanol (MeOH) and distilled water (dH_2O) by the method of maceration as described in our previous publication (Gezici and Sekeroglu, 2019b; Gezici, 2019a), and then the extracts were stored at -20°C until further analysis.

Free Radical Scavenging Activity

Antioxidant activities of the extracts were determined using *in vitro* 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) methods (Gezici et al., 2017; Sekeroglu et al., 2017; Gezici and Sekeroglu, 2019b). Ascorbic acid was used a commercial standard for DPPH assay, whilst Trolox was used a commercial standard for ABTS assay. The extracts and commercial antioxidant standards were dissolved in DMSO at different concentrations (100 to 1000 μg mL^{-1}) for the assays.

Human Cancer Cells and Anticancer Activity

A549 (lung carcinoma), MCF-7 (breast adenocarcinoma), and HeLa (cervical cancer) human cancer cells and non-tumorous HUVECs (human umbilical vein endothelial cells), obtained from the American Type Culture Collection (ATCC, USA) were used to evaluate the potential anticancer and cytotoxic activities of PVRH, PVK, and PVOR extracts from Pistachio. The A549 and HeLa cancer cells were cultured on Roswell Park Memorial Institute Medium (RPMI, ThermoFisher Scientific), and the other cells were grown in Dulbecco's modified Eagle medium (DMEM): Ham's F12 nutrient medium (1:1) (ThermoFisher Scientific) in the flasks at 37°C in a humidified CO_2 (5%) incubator. The cell growing conditions and supplements were used as same described in the previous publications (Gezici, 2018; Gezici, 2019a). In order to determine anticancer activities of the Pistachio extracts, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay was performed as described by Mosmann (1983) with minor modifications (Gezici, 2019a). The absorbance was measured at 570 nm with a Thermo Lab systems

408 Multiskan multiplate spectrophotometer, and the dose response curve was used to generate the IC_{50} (µg mL^{-1}) values for each cells.

Neuroprotective Activity

In the presented research, neuroprotective activities of Pistachio extracts were tested through enzyme inhibition against AChE (acetylcholinesterase), BChE (butyrylcholinesterase), and TYR (tyrosinase) enzymes. The assays were conducted in 96-well microplate using ELISA microplate reader (Thermo Lab systems 408 Multiskan). Galanthamine hydrobromide (Sigma, St. Louis, MO, USA) was employed as the reference for AChE and BChE, while α-Kojic acid (Sigma, St. Louis, MO, USA) was used as the reference for TYR. The extracts and reference standards were dissolved in DMSO at different concentrations, and the final concentration of the extracts and reference standards were adjusted to 1000 µg mL^{-1} and 100 µg mL^{-1}, respectively.

AChE and BChE inhibitory activity of the samples was measured by slightly modified spectrophotometric method of Ellman et al. (1961). All reagents, conditions and calculations were same as described in the previous publications (Senol et al., 2018; Gezici and Sekeroglu, 2019b). Briefly, electric eel AChE (EC 3.1.1.Sigma, St. Louis, MO, USA) and horse serum BChE (EC 3.1.1. Sigma, St. Louis, 7 MO, USA) were used, while acetylthiocholine iodide and butyrylthiocholine chloride (Sigma, St. Louis, MO, USA) were employed as substrates of the reaction. 5,5´-Dithio- bis(2-nitrobenzoic)acid (DTNB, Sigma, St. Louis, MO, USA) was used for the measurement of the anticholinesterase activity. For determination the inhibition of tyrosinase (EC 1.14.1.8.1, 30 U, mushroom tyrosinase, Sigma), the modified dopachrome method with L-DOPA as substrate was used as described Sekeroglu et al. (2012) previously.

Statistical Analyses

The data, obtained from the assays, were expressed as mean and standard deviation of mean (mean±SD). The percentage of enzyme inhibition on AChE, BChE and TYR was calculated as $[(Abs_{control} - Abs_{sample})/Abs_{control} \times 100]$, where $Abs_{control}$ value is the absorbance of the control solvent (blank), where Abs_{sample} is the absorbance of the tested sample (plant extract or positive control in the solvent) in the presence of enzyme. The measurements and calculations were evaluated by using Softmax PRO 4.3.2.LS software. P value of <0.05 was considered to be statistically significant, $p < 0.01$ and $p < 0.001$ were considered to be very significant.

Results and Discussion

Free Radical Scavenging Activity

Free radical scavenging activities of Pistachio extracts were determined against DPPH and ABTS radicals at various concentrations. Red hulls and kernels extracts of *P. vera* showed remarkable free radical scavenging activity, but oleo-gum resins extracts demonstrated moderate activity, comparing the standard antioxidants. The results were presented in Table 1 as (%) inhibition percentage at 1000 µg mL^{-1} concentration (Table 1).

Table 1. Free Radical Scavenging Activities of *P. vera* L. Extracts at 1000 µg mL^{-1}

Plant part	Extract type	DPPH[a]	ABTS[a]
Red hulls (PVRH)	Methanol	80.55±0.12***	86.92±0.10**
	Water	67.95±1.13**	92.04±1.06***
Kernels (PVK)	Methanol	56.08±0.52***	61.92±0.05**
	Water	44.61±0.49**	73.80±0.48***
Oleo-gum resins (PVOR)	Methanol	29.15±0.50***	40.18±1.07**
	Water	35.08±1.06**	47.21±0.55**
Ascorbic acid[b]		74.02±0.14	---
Trolox[c]		---	78.50±0.36

[a] The values were expressed as inhibition (%) ± standard deviation.
[b] Ascorbic acid; a commercial standard for DPPH assay.
[c] Trolox; a commercial standard for ABTS assay.
**p value of < 0.01; ***p value of < 0.001

As can be seen in the Table 1, all the Pistachio extracts displayed higher ABTS radical scavenging effects as compared to those of DPPH scavenging capacity at the tested concentrations. In both cases, PVRH extracts exerted the highest scavenging activity on DPPH and ABTS radicals, whilst PVOR extracts demonstrated the lowest ones with the inhibition percentage values ranged between 29.15±0.50 to 47.21±0.55. The highest DPPH scavenging activity was determined in the PVRH-MeOH extract (80.55±1.12% inhibition, $p < 0.001$), when the highest ABTS scavenging activity was found to belong to the PVRH-dH_2O extract with the 92.04±1.06% inhibition ($p< 0.001$), which was closely followed by the PVRH-MeOH extract (86.92±0.10% inhibition, $p< 0.01$).

DPPH and ABTS assays have been commonly used to determine the free radical scavenging activity of plant extracts and their pure compounds (Reddy et al., 2003; Farzaei et al., 2018). Based on the free radical scavenging results, red hulls of *P. vera* L. were found to have the most significant antioxidant potentials than the other parts of the plant, which may be due to the fact that its rich secondary metabolites components such as epicatechin, quercetin, naringenin, luteolin, kaempferol,cyanidin-3-O-galactoside and cyanidin-3-O-glucoside (Bozorgi et al., 2013; Seifaddinipour et al., 2018). The obtained results were consistent with previous works carried out to determine antioxidant potentials of different Pistachio species such as *P. atlantica, P. terebinthus, P. khinjuk,* and *P. lentiscus* (Rajaei et al., 2010; Hosseinzadeh et al., 2012; Bozorgi et al., 2013). Accordingly, the hull of Pistachio can provide significant benefits to cope with the oxidative-stress related diseases.

Anticancer Activity

Cancer prevention potentials of *P. vera* L. parts were assessed against A-549, MCF-7, and HeLa human cancer cells, compared to HUVEC control cells. The Pistachio extracts exhibited noteworthy cytotoxic potentials towards the tested cancer cells in a dose and time dependently; however, the IC_{50}

values were varied depending on the cancer cells. The results of anticancer activity were given in Table 2, regarding as IC_{50} (µg mL^{-1}) values after 72 hours at 200 µg mL^{-1} concentration.

In this assay, the parts of Pistachio known as waste parts (PVRH and PVOR) were found to possess higher cancer prevention potentials, compared to those of the part consumed as food (PVK). As summarized in the Table 2, all the tested parts of *P. vera* L. caused much more cytotoxicity on HeLa cells, following by MCF-7 cancer cells. Methanol extracts of *P. vera* L. were found higher anticancer activity than those of the water extracts against all the cells. The methanol extract of PVOR exerted the highest anticancer activity towards HeLa cells (IC_{50} = 18.50±0.85 µg mL^{-1}, p< 0.01), when PVK-dH_2O extract was found to have the weakest anticancer activity against A549 human cancer cells (IC_{50} = 268.66±1.02 µg mL^{-1}, p< 0.01).

Table 2. Anticancer activities of *P. vera* L. extracts against A549, MCF-7 ve HeLa human cancer cells

Human cancer cells	Plant Part		IC_{50} values[a] (µg mL^{-1})
A549	Red hulls	Methanol	191.04±0.18*
		Water	232.75±0.49**
	Kernels	Methanol	240.23±0.64*
		Water	268.66±1.02**
	Oleo-gum resins	Methanol	164.50±2.01**
		Water	187.28±0.16**
MCF-7	Red hulls	Methanol	90.16±0.38*
		Water	105.02±0.86*
	Kernels	Methanol	122.40±0.21**
		Water	130.01±0.60*
	Oleo-gum resins	Methanol	80.36±0.77**
		Water	88.92±1.14**
HeLa	Red hulls	Methanol	40.15±0.98**
		Water	34.20±0.20**
	Kernels	Methanol	46.48±0.55*
		Water	52.69±0.46*
	Oleo-gum resins	Methanol	18.50±0.85**
		Water	28.97±0.08**
Doxorubicin [b]			8.15±0.02
DMSO (dimethyl sulfoxide) [c]			0

[a] Values were expressed as IC_{50} ± SD from three independent experiment (n=3).
[b] Doxorubicin, positive control.
[c] DMSO; dimethyl sulfoxide, negative control.
*p value of < 0.05; **p value of < 0.01

In previous studies conducted with the other Pistachio species revealed anticancer properties of the Pistachio extracts against cancer cells. According to Rezaei et al. (2012), *P. atlantica* fruit extract were analysed for its anticancer activity on human colon carcinoma cells (HT29) and the extract were showed powerful growth inhibition in cancer cells, as compliant with the results obtained from the presented research (Rezaei et al., 2012). Dimas et al. (2009) revealed antitumor activities of the gum extracts obtained from *P. lentiscus* var. *chia* in colorectal cancer developed mice, the extracts also induced suppression of growth of human colorectal tumor xenografts (Dimas et al., 2009). In another research performed with oleoresin obtained from *P. vera* L. were tested against hepatocellular carcinoma, cervical cancer, and melanocyte cells and determined significant cytotoxic potential on the tested cells, which is more similar to the current results (Almehdar et al., 2012).

As previously reported, high antioxidant activity and rich polyphenolic content of the herbal extracts are known to be closely related to inhibit cancer and neurodegenerative diseases efficiently (Reddy et al., 2003; Tabatabaei-Malazy et al., 2013; Newman and Cragg, 2016; Roy et al., 2018; Gezici, 2019a; Gezici and Sekeroglu, 2019a). Terpenes and phenolic components are the main bioactive phytochemicals found in different parts of *P. vera* L. These components have been known to possess significant antioxidant and anti-inflammatory effects, and so they are probably responsible for preventing cancer, as demonstrated by previous researches (Rajaei et al., 2010; Bozorgi et al., 2013; Fathalizadeh et al., 2015; Das and Gezici, 2018; Seifaddinipour et al., 2018).

Neuroprotective Activity

Neuroprotective activity of the PVRH, PVK, and PVOR extracts obtained from *P. vera* L. were assessed through enzyme inhibition assays towards acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), and tyrosinase (TYR) enzymes at 100, 200, 400, 800, and 1000 µg mL^{-1} concentrations. As given in Figure 1, the dH_2O extracts of Pistachio exerted higher enzyme inhibitory effect against the tested enzymes than those of the MeOH extracts. Enzyme inhibitory potentials of the Pistachio parts on cholinesterase enzymes were resulted in the superiority of PVRH-dH_2O extract 81.50±0.08% inhibition on AChE, 62.96±1.01% inhibition on BChE, respectively (Figure 1).

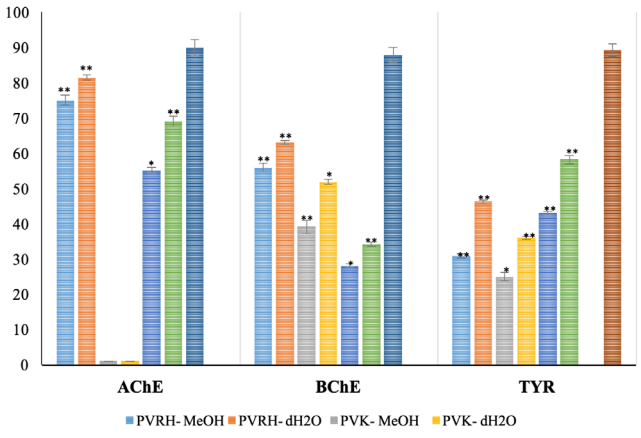

Figure 1. Enzyme Inhibition Capacities of P. vera L. Extracts against AChE, BChE and TYR

[PVRH: *P. vera* red hulls; PVK: *P. vera* kernels; PVOR: *P. vera* oleo-gum resins]

The values were presented as inhibition (%) ± standard deviation

*p value of < 0.05; **p value of < 0.01

In the contrary the inhibition on cholinesterase enzymes, PVOR-dH_2O extract was found to have the highest inhibitory effect on TYR enzyme (58.16±0.18%). PVK extracts inhibited BChE and TYR enzymes from moderate level to weak level, in which the higher cholinesterase inhibitory activity was observed against BChE (% inhibition from 39.10±0.12 to 51.94±0.68), compared to TYR (% inhibition from 25.03±1.01 to 36.04±0.65), whilst they demonstrated no inhibition against AChE enzyme even at the highest concentration (Table 3, Fig 1).

However, there have been a few studies focused on revealing anti-cholinesterase activity of the other Pistachio species, no study have been performed to screen anticholinesterase and anti-tyrosinase activities of different part of *P. vera* L. up to now. On the other hand, this is the first research that screened neuroprotective potentials of the extracts obtained from red hulls, kernels, and oleo-gum resins of *P. vera* L. In a previous work, aqueous extracts from *P. atlantica* and *P. lentiscus* leaves were determined regarding of their acetylcholinesterase inhibitory effects, and found as relatively weak AChE inhibitory activity (Benamar et. al., 2010). In another research on enzyme inhibitory effects of Pistachio species were performed using ethyl acetate and methanol extracts of the *P. terebinthus* kernels that showed no inhibitory activity against AChE and TYR, when they demonstrated inhibition on BChE at moderate levels (Orhan et al., 2012). These findings are consistent with the presented data for the kernel extracts.

On the basis of the findings obtained from the current work, the red hull part of the plant is seem to be a valuable agent for inhibition on AChE and BChE enzymes, while oleo-gum resin of Pistachio is a good candidate for inhibition against TYR enzyme. In fact, rich polyphenolic contents of *P. vera* L. are likely contribute to its remarkable neuroprotective capacity as reported previously (Rajaei et al., 2010; Hosseinzadeh et al., 2012; Fathalizadeh et al., 2015; Seifaddinipour et al., 2018).

Table 3. Neuroprotective Potentials of *P. vera* L. Extracts at 1000 µg mL^{-1}

Plant part	Extract type	% Inhibition ± SD [a]		
		AChE	BChE	TYR
Red hulls	Methanol	75.06±0.22**	56.01±0.90**	30.84±1.10**
	Water	81.50±0.08**	62.96±1.01**	46.32±0.08**
Kernels	Methanol	---[d]	39.10±0.12 **	25.03±1.01*
	Water	---[d]	51.94±0.68*	36.04±0.65**
Oleo-gum resins	Methanol	55.28±0.77*	28.13±0.98*	42.98±0.15**
	Water	69.12±0.94**	34.21±0.55**	58.16±0.18**
Galantamine [b]		90.04±0.86	87.94±0.20	---
α-Kojic acid [c]		---	---	89.35±0.18

[a] The values were given as inhibition (%) ± standard deviation (n=3).
[b] Galantamine; a commercial standard for AChE and BChE enzymes
[c] α-Kojic acid; a commercial standard for TYR enzyme.
[d] No inhibitory activity.
*p value of < 0.05; **p value of < 0.01

Conclusion

In the current research, anticancer, antioxidant and neuroprotective potentials of red hulls, kernels and oleo-gum resins obtained from Pistachio (*P. vera* L.) were analysed through *in vitro* test systems. Overall, the results obtained from this work showed that different parts of Pistachio could be a good candidate for cancer prevention and inhibition of the enzymes associated with pathogenesis of neurodegenerative diseases. As far as the literature survey, no study has been performed to examine anticancer and neuroprotective activities of the extracts obtained from different parts of Pistachio. Thus, this data could be the first report for the literature. The author suggest that Pistachio with whole part is a valuable natural source for curative purposes and further *in vivo* studies and clinical trials should be conducted to ascertain its bioactivity.

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Conflict of interests

No conflict of interest with the contents of this article.

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