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The Biological Activity; Cytotoxicity and Antioxidant Activity of *Jurinea brevicaulis*

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ABSTRACT

Jurinea brevicaulis is a perennial herbaceous plant belonging to the Asteraceae family. *J. brevicaulis* is an endemic genus and grows Erzincan and Gümüşhane provinces in Turkey. *Jurinea* species are known to have anticancer, antibacterial, antifungal and antioxidant effects. In this article, it is aimed to evaluate the antioxidant capacity and cytotoxic effects of *J. brevicaulis*. Results indicate that, TPC values were between 41.7 - 537.5 GAE µg g^{-1}, FRAP values were between 109.52 - 1076.2 µM Trolox equivalent g^{-1}, CUPRAC values were between 231.4 - 3083.3 µM Trolox equivalent g^{-1}, IC_{50} values in DPPH determination were between 0.0102 - 3.4174 mg mL^{-1}. The extracts caused cell death in a concentration-dependent manner in, IC_{50} values were calculated to be between 3.67-10.2 µg mL^{-1}. In conclusion, the cytotoxic effects in cancerous cells and the high antioxidant capacity indicates that *J. brevicaulis* could be an important herb in developing new drugs.

Research Article

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ÖZET

Jurinea brevicaulis, Asteraceae familyasına ait çok yıllık otsu bir bitkidir. *J. brevicaulis* endemik bir cinstir ve Türkiye'de Erzincan ve Gümüşhane illerinde yetişir. *Jurinea* türleri antikanser, antibakteriyel, antifungal, antioksidan etkiler gösterdiği bilinmektedir. Bu makalede, *J. brevicaulis*'in antioksidan kapasitesini ve sitotoksik etkilerini değerlendirmek amaçlanmıştır. Sonuçlar, TPC değerlerinin 41.7- 537.5 GAE ug g^{-1} arasında, FRAP değerlerinin 109.52- 1076.2 uM Troloks eşdeğeri g^{-1}, CUPRAC değerlerinin 231.4- 3083.3 uM Trolox eşdeğer g^{-1}, DPPH tayininde IC_{50} değerleri 0.0102- 3.4174 mg mL-1 arasında olduğunu göstermektedir. Ekstreler, konsantrasyona bağlı bir biçimde hücre ölümüne neden olmuştur, IC_{50} değerleri 3.67-10.2 ug mL^{-1} arasında hesaplanmıştır. Sonuç olarak, kanser hücrelerdeki sitotoksik etkiler ve yüksek antioksidan kapasite, *J. brevicaulis*'in yeni ilaçların geliştirilmesinde önemli bir bitki olabileceğini göstermektedir.

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INTRODUCTION

Herbs are used in almost all cultures as remedies under different names like traditional therapy, complementary therapy, and natural therapy (Singh, 2015; Acibuca and Bostan Budak 2018). Recently, the interest in herbal remedies increases dramatically in both developing and developed countries. WHO reported that about 70-80% of people preferred herbs as primarily health care products (Maiti et al., 2011). Reports show that the herbal medicinal preparations are more in demand than the main pharmaceutical products in Japan. It was estimated that more than 2.5 billion $ of income of United States in the mid 90's was due to herbal medicine sales. Studies from China show that about 40% of total medical consumption is attributed to traditional medicines. Plant derived substances were also 39% of the prescriptions in Colombia (Jiménez et al., 2015; Singh, 2015).

Turkey is the intersection point of the eastern Iran-Turan, the southern Mediterranean and the humid Euro-Siberian geographical regions. The intermixture of these three phytogeographic regions has led to a rich vegetation and herbs diversity especially in Eastern of Anatolia (Ozgokce and Ozcelik 2004; Kilic et al., 2013). This flora diversity offered resources for Anatolian medicine-culture. Studies show that the vast majority of Turkish people especially how living in rural areas use herbs traditionally under the name of folk medicine practices. Some of these herbs have been used in the development of many drugs in modern medicine (Faydaloğlu, 2011; Polat et al., 2013).

Jurinea brevicaulis is a plant belonging to the Asteraceae family, the second largest family of Turkish flora, which has the largest number of species in Turkey's Flora. One of the most important breeds of this family is *Jurinea Cass.* which contains about 200 species in total spread in Central Asia, Iran, Turkey and the Mediterranean basin. *J. brevicaulis* is one of the five Jurinea species endemic to Turkey (Dogan et al., 2011).

Jurine abrevicaulis is a perennial herbaceous plant that habitats on stony magmatic hills, steppes, and bare slopes at 1400-1900 m altitude. Its roots are erect and 15-20 cm in tall, the leaves attached to the stem and they are oblong-lanceolate at the base, petiolate in the middle, papillose-arachnoid at the top. The flowers are purplish-pink (Davis, 1975). *J. brevicaulis* grows in and around the Anatolian Dialogue, one of the major centers of endemism and considered as the hot spot of biodiversity in Turkey, and widely distributes in Erzincan and Gümüshane provinces (Figure 1) (Tubives; Dogan et al., 2007; Gemici et al., 2008).

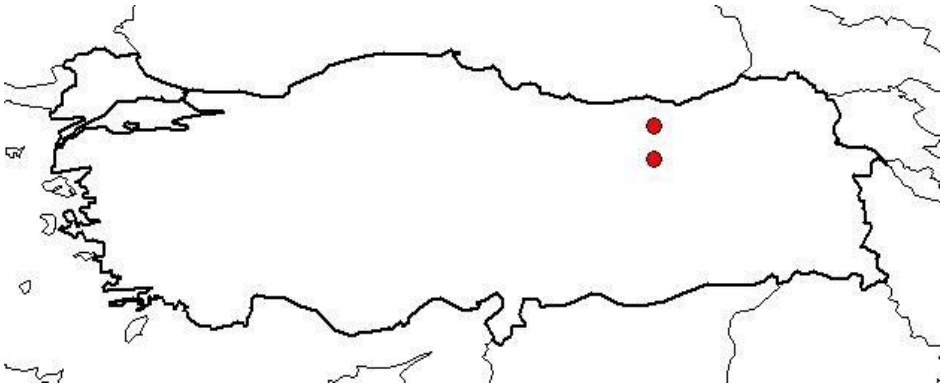

Figure 1: *J. brevicaulis'* distribution over Turkey. Herb spreads in Erzincan and Gümüşhane provinces (Tubives)
Şekil 1: J. brevicaulis'in Türkiye'de dağılımı; Erzincan ve Gümüşhane illerinde yayılması (Tubives)

Previous studies show that Jurinea species have been used traditionally as aphrodisiac and in the treatment of eye infections, fever, gout and rheumatism (Singh et al., 2016); And have different biological activities as antioxidant and anti-lipid peroxidation (Shah et al., 2014; Taherkhani 2015, Ayad et al., 2017), antibacterial (Dwivedi and Wagay, 2014; Ayad et al., 2017), antifungal and DNA Protection Activity (Singh et al., 2016) and *in vitro* cytotoxic potential against cancerous cell lines (Taherkhani and Rustaiyan 2016). However, there is no studies evaluate the biological activity of Turkey endemic *J. brevicaulis*; Therefore, as a preliminary study of antineoplastic activity, the cytotoxicity and the antioxidant activity were evaluated for methanol, water, chloroform and ethyl acetate *J. brevicaulis* extracts. For that, MTT assay was used in cytotoxicity evaluation while Total Phenolic Content Determination (TPC), ferric reducing antioxidant power (FRAP), cupric reducing antioxidant capacity (CUPRAC), and 2,2-diphenylpicrylhydrazyl (DPPH) radical scavenging activity assays were used to estimate the antioxidant activities.

Material and Method

Material

Acetic acid, acetonitrile, Dimethyl sulfoxide, Folin-Ciocalteu's, MTT dye, methanol, Trolox (6 hydroxy–2,5,7,8-tetramethylchroman 2-carboxylic acid) and TPTZ (2,4,6-tripyridyl-s-triazine) were purchased from Sigma Aldrich (St. Louis, MO, USA). All cell culture materials were purchased from Multicell Wisent (Quebec, Canada).

Herbal Extraction

Jurinea. brevicaulis were collected in July 2017 from the Erzincan (Turkey) and identified by Professor Ali KANDEMIR. The voucher specimens were kept in the herbarium of Erzincan University, Faculty of Science (Herbarium number: 10958). The roots and aboveground parts were dried in the shade, powdered in the grinder. 25 g of powder was extracted with 100 mL methanol, water, chloroform or ethyl acetate with continuous stirring for 24 h at room temperature. The extracts filtered using filter paper (Whatman No. 1) and were concentrated by a rotary evaporator at 40°C under reduced pressure.

Antioxidant Activity

DPPH• Radical Scavenging Activity

DPPH radical scavenging activity is based on the antioxidant's DPPH cation radical scavenging capacity (Molyneux, 2004). For that, 0.75 mL of DPPH reagent (0.1 mM in methanol) was mixed with 0.75 mL of the sample or standard and vortexed vigorously, incubated in the room temperature and darkness for 50 mins. The discoloration of DPPH was measured spectrophotometrically at 517 nm and the absorbances were plotted against the sample concentrations (mg mL^{-1}) (Figure 2). Median scavenging percentage SC_{50} values (mg sample per mL) were calculated using the equation obtained from the graph (Equation 1). Butylated hydroxytoluene (BHT) was used as a standard.

Equation 1: SC_{50} value = ((y/2) - n) / m)

Eşitlik 1: SC_{50} value = ((y/2) - n) / m)

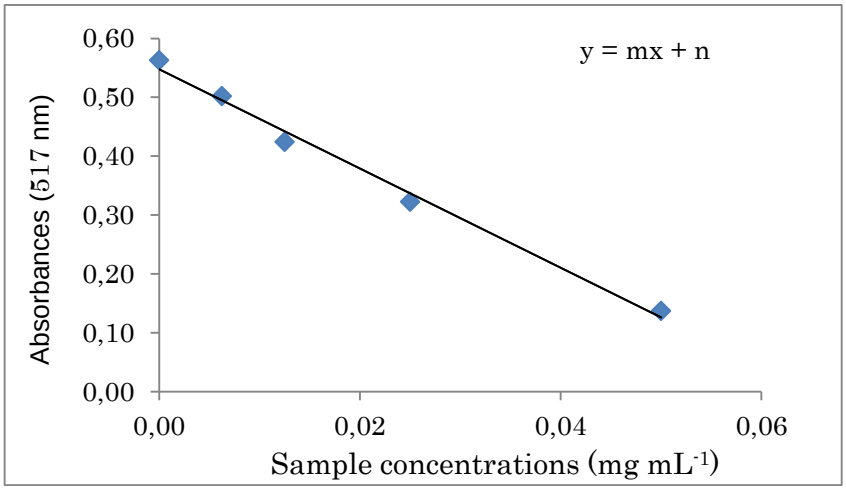

Figure 2: Example of a graph of absorbances againist sample concentrations for DPPH• Radical Scavenging Activity

Şekil 2: DPPH• Radikal Temizleme Aktivitesi için absorbanslara karşı numune konsantrasyonlarına ait bir grafik örneği

Total Phenolic Content (TPC)

The total phenolics amount in the extracts was estimated according to Folin-Ciocalteu procedure (Maiti et al., 2011). In alkaline medium, Folin-Ciocalteu reagent reacts with the phenolic compounds to form a blue colored complex, that could be measured by spectrophotometer. For that, 50 µL of the sample was mixed with 250 µL of 0.2 N Folin-Ciocalteu reagent and 750 µL of 7.5% sodium carbonate, incubated for 2 h at room temperature. Then the absorbance was measured at 765 nm spectrophotometrically. Gallic acid was used as a standard, and the total phenolics were expressed as µg of gallic acid equivalents (GAE) per g of sample.

Ferric Ion Reducing Antioxidant Power (FRAP)

To estimate the iron reducing capacities of the extracts (Korkmaz et al., 2014). 0.05 mL of the extracts was mixed with 1.5 mL of the freshly prepared FRAP reagent (25 mL of 0.3 M acetate buffer at pH 3.6 mixed with 2.5 mL of 10 mM 2,4,6-tripyridyl-S-triazine (TPTZ) solution in 40 mM HCl and 2.5 mL of 20 mM $FeCl_3.6H_2O$) and incubated at 25 ºC for 20 minutes. Spectrophotometry at 595 nm was used to measure the absorbance. Trolox was used as standard, FRAP values were expressed as µM Trolox equivalent per g (TE µM g^{-1}) of sample.

Cupric Reducing Antioxidant Capacity (CUPRAC)

Apak et al., (2006) method was used to investigate the reducing mass levels of antioxidant capacity (CUPRAC) of the extracts (Apak et al., 2006; Doğan et al., 2015). Briefly, 0.5 mL of the extracts was added to 1 mL of $CuCl_2$ solution ($1.0x10^{-2}$ M). After that, 1 mL of neocuproine solution ($7.5x10^{-3}$ M) and 1 mL of ammonium acetate buffer solution were added. The mixture incubated for 20 minutes at 25 ºC. Spectrophotometer at 450 nm was used to measure the absorbance. The CUPRAC values were expressed as µM Trolox equivalent per gram of sample.

Cytotoxic Activity (MTT Test)

The cytotoxic potential of *J. brevicaulis* was evaluated by MTT test which estimate the mitochondrial activity in the cells. In this test, the water soluble yellowish MTT dye metabolized to produce hydrophobic purple formazan crystals by the mitochondrial succinate dehydrogenase enzyme in the viable cells and the changes in color accept as a sign for the viability (Alley et al., 1988). For that, human lung cancer A549 cells (CRL-1571TM, ATCC®) were maintained in DMEM:

F12 Medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin, incubated at 37°C in 5% CO_2 humidified incubator. 96-well plates were used in this test and the cell density was 10^3 - 10^4 cells per well. The cells were exposed for 24 hours to *J. brevicaulis* extracts at concentrations between 3.12 - 100 µg mL^{-1}. After that, 30 µL of MTT solution (5 mg mL^{-1}) were added to each well, and incubated for farther 2 hours. Whereupon, the supernatant was removed, and the formazan crystals were dissolved in 100 µL DMSO. The optical density (OD) of formazan product was read at 590 nm (reference wavelength was 670 nm) using a microplate reader. The percentage of enzyme inhibition was calculated compared to the solvent control (1% DMSO) according to the formula below. The results were expressed as median inhibition concentration (IC_{50}), that the concentration of sample which responsible for a 50% inhibition of enzyme activity in the cells.

RESULTS

Antioxidant Activity

Several procedures are often used to elucidate the antioxidant potential of a substance or a complex mixture. For that, DPPH, CUPRAC, FRAP and TPC tests were used in this study to evaluate the antioxidant potential of *J. brevicaulis* extracts.

DPPH• Radical Scavenging Activity

Results indicate that all extracts have a concentration-dependent radical scavenging activity of DPPH and the SC_{50} was calculated to be 0.0102 – 3.4174 mg mL^{-1}. Compared to BHT (SC_{50} values were 0.0731, 0.0589 and 0.0325 at 1, 5 and 10 mg mL^{-1} respectively) and the other extracts the SC_{50} values indicate that methanol extract (at 10 mg mL^{-1}) has the lowest SC_{50} value (0.0102 ± 0.0008 mg mL^{-1}) and exhibits the highest antiradical activity against the DPPH free radical, while the chloroform extract of *J. brevicaulis* at a concentration of 1 mg mL^{-1} shows the lowest antiradical activity.

Total Phenolic Content (TPC)

The TPC of *J. brevicaulis* increases in concentration-dependent manner and ranges between 41.67 – 537.5 GAE µg g^{-1} (Table 1). Methanol and water extracts TPC values were higher than ethyl acetate and chloroform extracts.

Ferric Ion Reducing Antioxidant Power (FRAP)

The FRAP *J. brevicaulis* extracts found to be concentration dependent. FRAP values were calculated to be between 109.52 – 1076.19 TE µM g^{-1}. Methanol extract showed the highest antioxidant capacity, while chloroform extract had the lowest (Table 1).

Cupric Reducing Antioxidant Capacity

J. brevicaulis extracts gave a CUPRAC values with a total antioxidant capacity ranging between 231.43 and 3083.33 TE µM g^{-1}. The antioxidant capacity was increased in a concentration dependent manner. Methanol extract showed higher antioxidant capacity than aqueous extracts. Both water and methanol extracts showed a higher activity than chloroform and ethyl acetate extracts.

Cytotoxic Activity

Different concentration between 3.12 – 100 µg mL^{-1} *J. brevicaulis* extracts' were evaluated for the cytotoxic potential by MTT assay in A549 human lung cancer cells. Results indicate a concentration dependent cytotoxicity for all the extracts. IC_{50} values calculated to be 3.67 – 10.19 µg mL^{-1} (Table 2). Chloroform extract show the highest cytotoxicity while water extracts show the lowest.

Table 1. The antioxidant activities of *J. brevicaulis* extracts
Çizelge 1. J. brevicaulis ekstrelerinin antioksidan aktiviteleri

extracts	***ekstreler***	*mg mL^{-1}*	***TPC*** *GAE µg g^{-1}*	***FRAP*** *(TE µM g^{-1})*	***CUPRAC*** *(TE µM g^{-1})*	***DPPH*** *(mg mL^{-1})*
Methanol extract	*Metanol ekstraktı*	1	122.08 ± 1.61	410.48 ± 2.52	776.67 ± 2.19	0.3151 ± 0.0038
		5	321.25 ± 2.48	659.05 ± 4.25	2137.62 ± 7.64	0.0511 ± 0.0011
		10	537.50 ± 3.63	1076.19 ± 5.65	3083.33 ± 8.21	0.0102 ± 0.0008
Water extract	*Su ekstraktı*	1	56.67 ± 0.75	201.90 ± 1.09	748.10 ± 2.07	0.4721 ± 0.0045
		5	168.33 ± 1.97	519.52 ± 3.36	1699.52 ± 5.67	0.2618 ± 0.0024
		10	446.67 ± 2.93	949.05 ± 5.17	2236.67 ± 7.83	0.1420 ± 0.0023
ethyl acetate extract	*Etil asetat ekstraktı*	1	58.75 ± 0.59	117.62 ± 1.38	368.10 ± 2.03	2.6436 ± 0.0133
		5	166.25 ± 1.42	331.43 ± 2.47	532.86 ± 3.45	2.0135 ± 0.0102
		10	261.25 ± 1.50	578.57 ± 3.49	866.67 ± 4.31	1.5046 ± 0.0097
Chloroform extract	*Kloroform ekstraktı*	1	41.67 ± 0.61	109.52 ± 1.32	231.43 ± 2.30	3.4174 ± 0.0178
		5	158.33 ± 1.34	265.71 ± 2.43	292.86 ± 2.14	2.6067 ± 0.0132
		10	245.83 ± 2.31	452.86 ± 3.45	367.14 ± 3.26	2.0307 ± 0.0104

Table 2. The cytotoxic activity of *J. brevicaulis* by MTT test in A549 cell line.
Çizelge 2. A549 hücre hattında MTT testi ile J. brevicaulis'in sitotoksik aktivitesinin değerlendirmesi.

Extract / ***Ekstreler***	Concentration (µg mL^{-1}) (*Konsantrasyon (µg mL^{-1})*)						
	3.125	6.25	12.5	25	50	100	IC_{50}
Methanol / *Metanol*	41.47	56.56	70.25	73.40	75.15	77.32	5.22
Water / *Su*	36.38	46.42	61.21	64.77	70.44	82.80	10.19
Ethyl acetate / *Etil asetat*	36.67	55.02	67.35	72.39	83.22	84.43	5.55
Chloroform / *Kloroform*	42.85	60.96	74.42	77.03	84.07	84.87	3.67

DISCUSSION

A high ratio of world's population uses the herbal medicinal products. In both the Eastern and Western cultures herbal products have been using as remedies for hundreds of years, Chinese medicine is an example for intensive use of herbs the treatment of many diseases including cancer (Chan, 2003; Lau et al., 2004; Pan et al., 2004).

People are exposed to the harmful effects of reactive oxygen species (ROS) by many sources. The endogenous defense system of the human body shows weak effects against ROS, depending on both aging and environmental factors. As a result, many of the components in the body are damaged causing the degenerative disease to appear. For this reason, the demand for exogenous antioxidants is gradually increasing in order to help the body to cope with oxidative stress (Zaporozhets et al., 2004).

Oxidative stress is known to be associated with many disorders and diseases such as cancer, atherosclerosis, aging, inflammation, Parkinson, and Alzheimer's (Gupta et al., 2014, Yalcin et al., 2017). ROS affects both membrane-bound protein kinases, growth factors and receptors, as well as causing signal transduction, oncogene activation, inactivation of suppressive genes and cancer formation (Yokus and Cakır, 2012). Polyphenolic compounds exhibit strong antioxidant properties. Thus, they can prevent the development of cancer by eliminating the harmful effects of ROS. Furthermore, flavonoids possess biomolecular activities such as apoptosis rate increase, cell proliferation inhibition, lipid peroxidation inhibition, angiogenesis inhibition, DNA oxidation inhibition (Chahar et al., 2011, Yalcın et al., 2017). Most of the Jurinea species are rich in flavonoids such as sesquiterpene lactones and triterpenes (Shah et al., 2014, Singh et al., 2016, Ayad et al., 2017). In phytochemical studies, Jurinea species have been found to contain flavonoids such as apigenin, catechin, caffeic acid and routine (Shah et al., 2014, Ayad et al., 2017), That known for their anticancer activities in various cancer cell lines (Yin et al., 1999, Wenzel et al., 2000, Chahar et al., 2011).

Taherkhania and Rustaiyan (2016) show that shirazolide extracted from *Jurinea leptoloba* show cytotoxicity in HeLA cells (IC_{50} value was 2.8 µg mL^{-1}). As the cytotoxicity in normal lymphocyte (IC_{50}, 9202.2 µg mL^{-1}) was lower; they concluded shirazolide and so *J. leptoloba* are promising in antineoplastic chemotherapy development. In other study, Taherkhani (2015) evaluated the antioxidant and cytotoxicity of the essential oil of *J. leptoloba* DC; The results suggest *J. leptoloba* essential oil has moderate antioxidant as the TPC was 16.53 GAE µg mg^{-1} oil, DPPH IC_{50} value was 24.50 mg mL^{-1}, and could be used for anticancer development especially that the essential oil show cytotoxicity in Hela cells (IC_{50} was 290.7 µg mL^{-1}) and normal lymphocyte (IC_{50} 2901 µg mL^{-1}).

Jurinea dolomiaea Roots were shown to have an antioxidant activity when evaluated by TPC and total flavonoid contents diverse antioxidant assays (Shah et al., 2014). In a study evaluated *Jurinea humilis* for the antimicrobial and antioxidant activities, it was indicated that *J. humilis* has a good antioxidant (DPPH assay IC_{50} was 0.16 mg mL^{-1}; TPC, 169.14 GAE mg g^{-1}) and antimicrobial properties because of the high amount of phenolic and flavonoid contents (Ayad et al. 2017). Similarly, *Jurinea dolomiaea* found to have antibacterial activity (Dwivedi & Wagay 2014). Öztürk et al (2011) evaluated the antibacterial, anticholinesterase and antioxidant activities of *Jurinea consanguinea* by TPC, total flavonoid contents, b-carotene bleaching and DPPH free radical scavenging assays. While their results indicated insignificant antibacterial activities compared with drugs in use, they highlighted a potent anticholinesterase and antioxidant activities. In this work, *J. brevicaulis* has been found to have antioxidant activity by TPC, FRAP, CUPRAC and DPPH Radical scavenging antioxidant activity determination assays. A difference in antioxidant activities between the extracts was detected, While the methanol extract has the higher activities, chloroform and ethyl acetate have lowest. Besides that, antioxidant activities for all extracts found to be concentration dependent. The results of cytotoxicity test show that *J. brevicaulis* extracts induced concentration-dependent cytotoxicity with IC_{50} values arrange between 3.67-10.2 µg mL^{-1}.

In conclusion, the cytotoxic effects in cancerous cells and the high antioxidant capacity indicates that *J. brevicaulis* could be an important herb in the developing of new drugs. In this context, more pharmacognostical, *in vivo* and *in vitro* studies are required to obtain the active compounds of *J.*

brevicaulis, investigate its pharmacological effects and to evaluate its safety.

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Author Contributions:

All authors contributed substantially to the manuscript and have met the criteria for authorship.

Competing Interests:

The authors declare that there are any competing interests.

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