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ORIGINAL ARTICLE

In silico Studies on the Therapeutic Potential of Novel Marker Compounds Isolated from Chemically Modified Bioactive Fraction from *Curcuma longa* (Non-carbonyl *Curcuma longa*)

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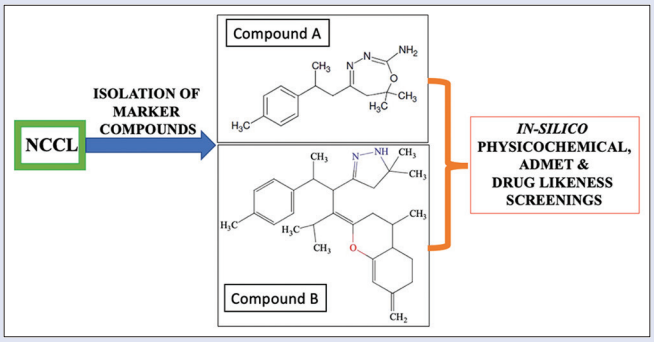
ABSTRACT

Background: *Curcuma longa*, a perennial herb, is a member of the *Zingiberaceae* (ginger) family is described to possess a broad spectrum of biological activities. Herbal medicament (HM) or curcuma oil is a bioactive standardized hexane-soluble fraction of *C. longa* and is established for its neuroprotective effect. HM was modified chemically to unfasten compounds containing carbonyl group in it resulting in a bioactive non-carbonyl *C. longa* (NCCL). **Objectives:** In the present study, novel marker compounds (A and B) have been successfully isolated from NCCL and their various *in silico* traits and interactions were studied. **Materials and Methods:** Marker compounds A and B were characterized utilizing various spectroscopic data (one-dimensional [1D]/2D Nuclear Magnetic Resonance (NMR), mass spectrometry, and infrared). Isolated compounds were subjected to *in silico* computational tools for predicting their drug-likeness, pharmacokinetic, pharmacodynamic properties. **Results:** Both compounds A and B flaunted drug-like properties by following the standard descriptors along with good *in silico* absorption. **Conclusion:** Novel marker compounds A and B were successfully isolated from NCCL and fully characterized utilizing spectroscopic techniques. Both the compounds displayed good drug-like properties.

Key words: Absorption, distribution, metabolism, excretion, and toxicity, *Curcuma longa,* drug likeness, *in silico* studies, isolation, non-carbonyl *C. longa*

SUMMARY

- Two novel marker compounds A and B were successfully isolated from non-carbonyl *Curcuma longa* and were characterized using various spectroscopic techniques. Both the compounds showcased drug-like properties.



Abbreviations used: NCCL: Non-carbonyl *Curcuma longa*; HM: Herbal medicament; MS: Mass spectrometry; IR: Infrared; MI: Myocardial infarction; TNF-α: Tumor necrosis factor-alpha; IL: Interleukin; IFN: Interferon; CK-MB: Creatine kinase myocardial band; HPLC: High-performance liquid chromatography; ACN: Acetonitrile; HRMS: High-resolution mass spectrometry; PDA: Photodiode-array; TLC: Thin-layer chromatography; CSIR: Council of Scientific and Industrial Research.

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INTRODUCTION

Nature is one of the most pronounced synthetic chemists, and plants are next to a countless pool of charming chemical integrants with actual and likely outcome on the human body. The demand of plants for medicines throughout the world still significantly surpasses the use of prevalent synthetic drug.[1] *Curcuma longa* belongs to the *Zingiberaceae* family and has been ritually employed in ayurvedic medication and in the preparation of food.[2] It embraces assorted potent constituents such as phenols, tannins, alkaloids, saponins, flavonoids, curcuminoids, glycosides, and various volatile oils comprising various sorts of sesquiterpenes owing neuroprotective, anti-inflammatory, antithrombotic, and antiproliferative activities.[3-10]

Herbal medicament (HM) or curcuma oil is a potent hexane-soluble extract of *C. longa* rhizomes, developed by Central Drug Research Institute, India, as an anti-stroke agent.[11] It has displayed promising neuroprotective pursuit in neurovascular disorder, and it was licensed to Themis Medicare Ltd., Mumbai, for additional development as an anti-stroke vehicle. HM has been described to possess antimicrobial, insecticidal, antioxidant mosquitocidal, and anti-cancer activities.[3]

Leaning on the wide therapeutic attire of *C. longa*, it was thought

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worthwhile to remove carbonyl fraction from HM to obtain a non-carbonyl *C. longa* (NCCL), herein referred as NCCL having compounds such as zingiberene, curcumene, β-bisabolene, curzerene, β-sesquiphellandrene, and residual ar-turmerone. It was detected that even at a lower dose against endothelial-mediated inflammation in myocardial infarction/reperfusion (RP) induced rats, NCCL is more potent than its parent HM and its bioavailability is indeed superior than HM. It remarkably decreased the inflammatory cytokine mediators (tumor necrosis factor-alpha [TNF-α], interleukin [IL]-6, interferon-γ), serum creatine kinase myocardial band levels, plasma endothelial microparticle level in addition to improvement in the endothelial functionality.[12] The role of NCCL in anti-inflammatory and cytotoxic activity for leukemia and sepsis was additionally gauged resulting in a significant decrease of INF-α and IL-1β production in THP-1 cells of mice and human whole blood.[13] Furthermore, NCCL fraction having residual components emerged as a potent anti-cancer agent.[14]

Therefore, the present study was aimed to isolate and characterize these novel marker compounds A and B from NCCL. We also investigated its *in silico* physico-chemical, pharmacokinetic, pharmacodynamic traits along with their drug-likeness scores.

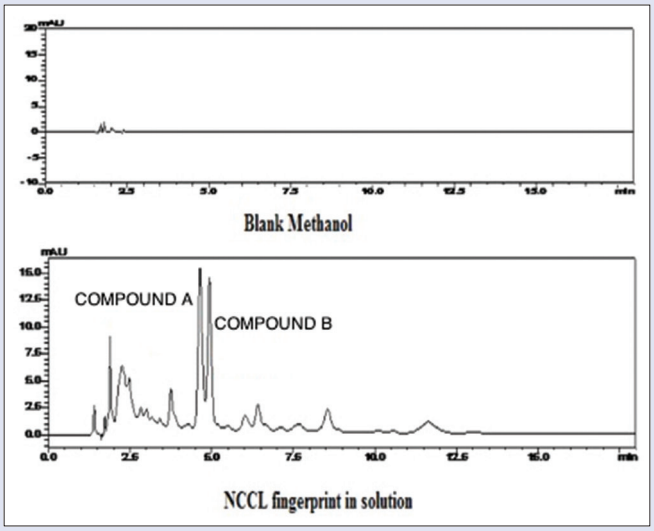

Figure 1: High-performance liquid chromatography fingerprint of non-carbonyl *Curcuma longa* in solution

MATERIALS AND METHODS

All chemicals purchased from Aldrich were of analytical grade and used without purification. HM fraction was prepared in the Medicinal and Process Chemistry Division of CDRI, Lucknow, India. Milli-Q pure water was procured from a Millipore Elix water purification system (Millipore India Pvt. Ltd., New Delhi, India). Methanol and acetonitrile (ACN) of high-performance liquid chromatography (HPLC) grade were purchased from Merck Ltd. (Mumbai, India). Infrared (IR) spectra were recorded using KBr discs on a Perkin Elmer Fourier transform (FT)-IR RX1 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on 400 MHz Bruker NMR spectrometers; chemical shift (δ) is reported in ppm using tetramethylsilane as an internal reference. Electrospray ionization-mass spectrometry (MS) was recorded on Thermo LCQ Advantage Max-IT. High-resolution mass spectrometry (HRMS) was recorded by quadrupole–time-of-flight mass spectrometer.

Preparation of non-carbonyl *Curcuma longa* extract

NCCL was prepared from hexane-soluble fraction of *C. longa* according to our reported method.[14]

Chromatographic method for fingerprinting of non-carbonyl *Curcuma longa*

Waters HPLC (Milford, MA, USA) system used was equipped with an autosampler injector (Model 2707, Waters), a binary gradient pump (model 515, Waters), and a diode array detector (Model 2998, Waters). For data acquisition, Waters HPLC interface and Empower 2 software were appraised. The analytical column RP-18e B LiChrospher® (250 mm × 4 mm, 5 µm, Merck, Germany) maintained at 30°C ± 3°C was utilized for this study. The mobile phase consisted of 70:30 v/v; ACN water was used as a mobile phase which was degassed before analysis using a Millipore vacuum pump. The flow rate was conserved at 1.0 mL/min, and the injection volume was 20 µL. The column effluent was tracked at 220 nm and 254 nm (photodiode-array detection) with 30 min as total runtime and shown in Figure 1.[14]

Isolation and identification of active marker compounds (A and B) from non-carbonyl *Curcuma longa*

The marker compounds A and B were separated as per our reported methods;[14,15] briefly, NCCL (200 mg) was dissolved in 5 mL ACN with few drops of water, and this mixture was injected onto a prep HPLC column C_{18} (250 mm, 25 mm, 15 µm, Phenomenex). The peaks were monitored at 220 and 254 nm. The flow rate was maintained at about 12 mL/min with isocratic flow of ACN and water (50:50 v/v). The fractions were collected according to their ascent in absorbance. The fractions containing compounds A and B were separated and then concentrated. Their purity was further established by thin-layer chromatography (TLC) and HPLC. Both the isolated novel marker compounds were found to be >98% pure. Compounds A and B were characterized by employing different spectral techniques such as FTIR, ^{1}H and ^{13}C NMR, and mass.

Method of Computation: *In silico* study

These newly isolated novel marker compounds A and B were evaluated for their drug-likeness scores employing the software from Molsoft server (http://www.molsoft.com). physico-chemical, pharmacokinetic, and pharmacodynamic, i.e., ADMET traits (absorption, distribution, metabolism, excretion, and toxicity) and drug-likeness violations of the compounds A and B were analyzed using Swiss ADMET web interface, developed, and maintained by the Molecular Modeling Group of the Swiss Institute of Bioinformatics (http://www.sib.swiss) and ProTox-II, a virtual laboratory for the prediction of toxicities of small molecules.

RESULTS

Compounds A and B [Figure 2] were isolated from NCCL by preparative HPLC. The fractions containing marker compounds were separated and concentrated under vacuum. These marker compounds are already reported in our previous communications.[14,15] The marker compound A was characterized as 7, 7-dimethyl-5-(2-p-tolylpropyl)-6,7-dihydro-1,3,4-oxadiazepin-2-amine and compound B as (E)-5,5-dimethyl-3-(5-methyl-4-(4-methyl-7-methylene-3,4,4a, 5,6,7-hexahydro-2H-chromen

-2-ylidene)-2-p-tolylhexan-3-yl)-4,5-dihydro-1H-pyrazole by utilizing various spectral techniques such as FTIR, ^{1}H and ^{13}C NMR, and mass. The purity of both compounds was checked by TLC and HPLC and was found >98% pure.

Compound A 7,7-dimethyl-5-(2-p-tolylpropyl)-6,7-dihydro-1,3,4-oxadiazepin-2-amine: $C_{16}H_{23}N_3O$; Light yellow oil; IR (KBr) (cm^{-1}): 3411.7, 3015.2, 1667.2,1564.5, 1514.7, 1448.0, 1216.1, 1054.7, 759.7, 669.1, 544.7. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.13(d, 2H, J = 7.68), δ 7.08(d, 2H, J = 7.56), δ 5.93 (S, 2H), δ 3.01 (dd, 1H, J = 6.90), δ 2.5 (m, 4H), δ 2.24(s, 3H), δ 1.31 (s, 3H), δ 1.23(s, 3H), δ 1.18 (d, 3H, J = 6.72). ^{13}C NMR (400 MHz, DMSO-d_6): δ_C 155.41, 153.28, 142.96, 135.04, 128.86, 126.69, 61.66, 50.85, 37.98, 36.55, 26.00, 25.78, 22.29, 20.59. Mass: *m/z* 274.5 (M^++1), 275.6 (M^++2), HRMS: *m/z* 274.1932 (M^++1), 275.1956 (M^++2).

Compound B, (E)-5,5-dimethyl-3-(5-methyl-4-(4-methyl-7-methylene-3,4,4a, 5,6,7-hexahydro-2H-chromen-2-ylidene)-2-p-tolylhexan-3-yl)-4,5-dihydro-1H-pyrazole: $C_{30}H_{42}N_2O$; Light yellow oil; IR (KBr) (cm^{-1}): 3685, 3297, 3021, 2927, 2856,2401, 1733, 1635, 1524, 1424, 1215, 1110, 1024, 928, 759, 670, 627, 496;. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.02 (4H, s), 5.95 (1H, s), 5.22 (2H, s), 4.83 (1H, s), 4.66 (1H, s), 3.16–3.24 (1H, m), 2.92 (1H, s), 3.30–2.70 (4H, m), 2.24 (1H, s), 2.23 (3H, s), 2.13 (1H, s), 2.00 (4H, m), 1.78 (1H, s), 1.58 (1H, s), 1.01–1.37 (16H, m); ^{13}C NMR (400 MHz, DMSO-d_6): δ_C 175.65, 157.53, 143.67, 135.54, 129.16, 129.09, 126.75, 126.66, 124.10, 115.03, 58.14, 53.40, 52.68, 38.95, 37.59, 35.32, 34.98, 29.68, 27.61, 27.44, 27.33, 22.68, 22.50, 22.40, 21.97, 20.94, 20.69. HRMS *m/z* 447.3371.

These isolated and characterized novel marker compounds A and B were evaluated for their *in silico* physico-chemical, pharmacokinetic/pharmacodynamic ADMET, and drug-likeness traits.

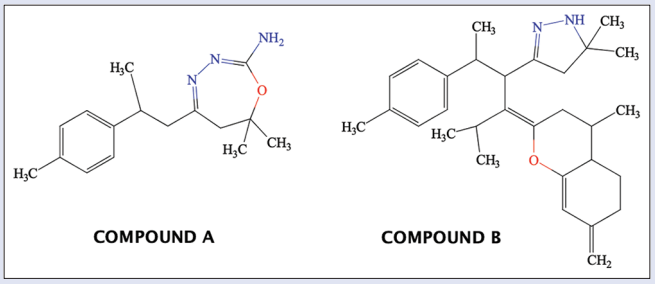

Figure 2: Structure of isolated novel marker compounds A and B from non-carbonyl *Curcuma longa*

Various physico-chemical parameters, namely molecular weight, number of rotatable bonds, molar refractivity, number of specific atom class, lipophilicity, and water solubility, were described. Topological polar surface area (TPSA), which is a very effective physiochemical variable, is gauged for evaluating the drug transport traits. The predicted % absorption was also computed for these compounds utilizing the following equation, i.e., % Absorption (ABS) =109−(0.345 × TPSA).[16,17] These physico-chemical properties are documented in Table 1. The bioavailability radar of compounds A and B is displayed in Figure 3 where the pink zone represents the optimal range for properties such as lipophilicity, flexibility, size, saturation, polarity, and solubility.

The drug-likeness forecast was also done depending on five different rules, namely Lipinski,[18,19] Ghose *et al.*,[20] Veber *et al.*,[21] Egan *et al.*,[22] and Muegge *et al.*,[23] along with drug-likeness, and the bioavailability scores are given in Table 2.

Forecasted pharmacokinetic/pharmacodynamics, ADMET attributes of the tested compounds A and B are given in Table 3.

DISCUSSION

Compound A, 7,7-dimethyl-5-(2-p-tolylpropyl)-6,7-dihydro-1,3,4-oxadiazepin-2-amine, and compound B, (E)-5,5-dimethyl-3-(5-methyl-4-(4-methyl-7-methylene-3,4,4a, 5,6,7-hexahydro-2H-chromen-2-ylidene)-2-p-tolylhexan-3-yl)-4,5-dihydro-1H-pyrazole, were isolated fromNCCL by preparative HPLC. In our previous communications, we reported these novel marker compounds A and B to be the cyclized products[14,15] and characterization was done on basis of various spectroscopic techniques.

After successful isolation and characterization of compounds A and B, we performed *in silico* predictive studies.

The physico-chemical properties state that the molecular formula of the compounds A and B is $C_{16}H_{23}N_3O$ and $C_{30}H_{42}N_2O$, respectively. The molecular weight was 273.37 and 446.67 g/mol, respectively. The fraction of carbon atoms in the sp^3 hybridization for A was 0.50 and B was 0.57. The number of hydrogen bond acceptors was 3 and 2, respectively, while the number of hydrogen bond donors was 1 for both the compounds. The molar refractivity was 90.57 and 149.21, respectively, for compounds A and B. The TPSA was found to be 59.97 and 33.62 A°, respectively, and the percent absorption was highest in compound B, being 97.40 as compared to compound A which is 88.31. From the log *P* values, it can be indicated that the compounds A and B are having good lipophilic character. The water solubility from log S depicts that both the compounds belong to moderately water-soluble class.

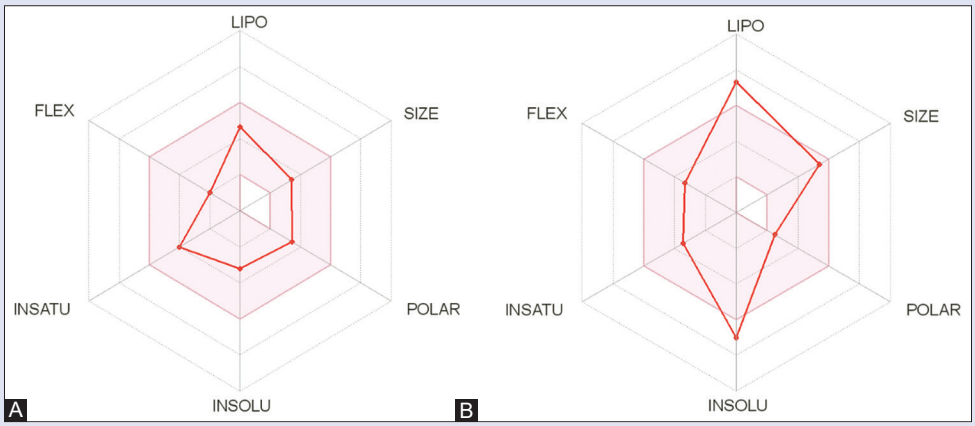

Figure 3: Bioavailability Radar of the tested isolated novel marker compounds A and B from non-carbonyl *Curcuma longa*

Table 1: Physico-chemical properties of the novel marker compounds isolated from non-carbonyl *Curcuma longa*

Compound number	Mol. formula	Mol. weight	Fraction Csp3[a]	HBA[b]	HBD[c]	iLogP[d]	MR[e]	Log *S*[f]	TPSA[g]	*In silico* absorption (%)
A	$C_{16}H_{23}N_3O$	273.37	0.50	3	1	2.65	90.57	S	59.97	88.31
B	$C_{30}H_{42}N_2O$	446.67	0.57	2	1	4.75	149.21	PS	33.62	97.40

[a]The ratio of sp^3 hybridized carbons over the total carbon count of the molecule, [b]Number of hydrogen bond acceptors, [c]Number of hydrogen bond donors, [d]Lipophilicity, [e]Molar refractivity, [f]Water solubility (SILICOS-IT; S=Soluble, PS=Poorly soluble), [g]Topological polar surface area (Å^2)

Table 2: Drug-likeness prediction of the novel marker compounds isolated from non-carbonyl *Curcuma longa*

Compound number	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability score	Drug-likeness score
A	Yes	Yes	Yes	Yes	Yes	0.56	−0.24
B	Yes, 1 violation	No, 3 violations	Yes	No, 1 violation	No, 1 violation	0.55	−0.67

Table 3: Absorption, distribution, metabolism, excretion, and toxicity properties of the novel marker compounds isolated from non-carbonyl *Curcuma longa*

Compound number	ADMET properties									
	Glabs[a]	BBB permeant[b]	Pgp substrate[c]	CYP1A2 inhibitor[d]	CYP2C19 inhibitor[e]	CYP2C9 inhibitor[f]	CYP2D6 inhibitor[g]	CYP3A4 inhibitor[h]	Log K_p[i]	LD_{50} (mg/kg)
A	High	Yes	No	No	Yes	No	No	No	−6.11	1100
B	Low	No	Yes	No	No	Yes	No	Yes	−3.83	2000

[a]Gastrointestinal absorption, [b]Blood-brain barrier permeant, [c]P-glycoprotein substrate, [d]CYP1A2: Cytochrome P450 family 1 subfamily A member 2 (PDB: 2HI4), [e]CYP2C19: Cytochrome P450 family 2 subfamily C member 19 (PDB: 4GQS), [f]CYP2C9: Cytochrome P450, family 2, subfamily C, member 9 (PDB: 1OG2), [g]CYP2D6: Cytochrome P450 family 2 subfamily D member 6 (PDB: 5TFT), [h]CYP3A4: Cytochrome P450 family 3 subfamily A member 4 (PDB: 4K9T), [i]Skin permeation in cm/s. ADMET: Absorption, distribution, metabolism, excretion, and toxicity

The bioavailability radar of compounds A and B displayed that the pink area is the appropriate physico-chemical stretch for oral bioavailability where the following traits were taken into contemplation as lipophilicity, flexibility, size, saturation, polarity, and solubility. The lipophilicity of the molecule log *P* can lie between −0.7 and +5.0. The molecular weight should be between 150 g/mol and 500 g/mol. The TPSA bounds from 20 to 130 A°. The range of insolubility studied using log S Estimated Solubility (ESOL) comes between 0–6 and 0–9 rotatable bonds. The unsaturation fraction ranges from 0.25 to 1.0, pointing out that the fraction of carbon atoms in the sp^3 hybridization should not be <0.25.

Drug-likeness parameter is high for compound A as it follows all the rules, namely Lipinski, Ghose, Veber, Egan, and Muegge rule, with the bioavailability and drug-likeness score of 0.56 and −0.24, respectively. Compound B has favorable drug-like properties as it like a drug according to Lipinski and Veber, but its drug likeness is rejected by Ghose, Egan, and Muegge with more than one violation of the mentioned rules, though the bioavailability and drug-likeness scores are good to moderate being 0.55 and −0.67, respectively.

The compound A is forecasted with high gastrointestinal absorption, blood–brain barrier permeant, and P-gp substrate noninhibitor. While the predictions for compound B were just the opposite of the predictions obtained for compound A i.e compound B has low gastrointestinal absorption, no blood-brain barrier permeation and it is a P-gp substrate inhibitor. Compound A only inhibits the Cytochrome P450 family CYP2C19, while Compound B is predicted to inhibit only CYP2C9 and CYP3A4. The skin permeability coefficient log Kp (with Kp in cm/s) values indicated that the tested compounds A and B possess low-to-moderate skin permeation, respectively. Compound A is predicted to be harmful if swallowed (class 4) in nature, while compound B fall in Class 5 that it may be harmful if swallowed. Both the compounds emerged as non-toxic in AMES test and are non-carcinogenic in nature.

CONCLUSION

To conclude, we herein this study reported the synthesis of a novel chemically modified bioactive fraction from HM (NCCL) and isolation and characterization of novel marker compounds A, 7,7-dimethyl-5-(2-p-tolylpropyl)-6,7-dihydro-1,3,4-oxadiazepin-2-amine, and compound B, (E)-5,5-dimethyl-3-(5-methyl-4-(4-methyl-7-methylene-3,4,4a, 5,6,7-hexahydro-2H-chromen-2ylidene)-2-p-tolylhexan-3-yl)-4,5-dihydro-1H-pyrazole. Moreover, these isolated marker compounds have undergone an *in silico* analysis to explore their molecular and ADMET attributes. Both compounds A and B satisfactorily met the conditions to be like a drug candidate and emerged to be non-carcinogenic in nature according to some of the described rules. Meanwhile, compound B emerged as a P-gp substrate and Cytochrome P450 family CYP2C9 and CYP3A4 inhibitor. The % absorption was higher in compound B, i.e., 97.40, while for compound A, it was 88.31.

Our future research work is to evaluate their *in vitro* and *in vivo* therapeutic potentials and study the in-depth mechanistic aspects utilizing these results of isolated marker compounds from NCCL.

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Conflicts of interest

There are no conflicts of interest.

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