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Laboratory Experiment

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Integration of Nanoparticle-Based Paper Sensors into the Classroom: An Example of Application for Rapid Colorimetric Analysis of Antioxidants

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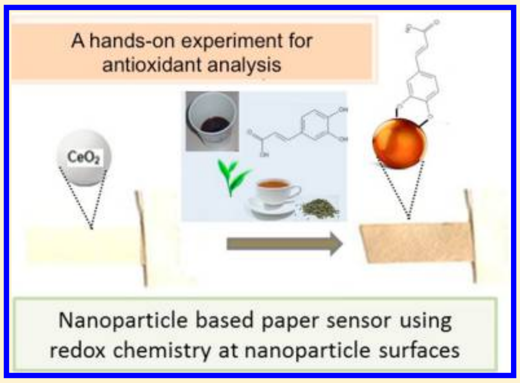
Ⓢ *Supporting Information*

ABSTRACT: We describe a laboratory experiment that employs the Nanoceria Reducing Antioxidant Capacity (or NanoCerac) Assay to introduce students to portable nanoparticle-based paper sensors for rapid analysis and field detection of polyphenol antioxidants. The experiment gives students a hands-on opportunity to utilize nanoparticle chemistry to develop their own devices to test antioxidant-containing solutions, such as tea and other beverages, for polyphenolic content, a characteristic likely correlated with health benefits. The method utilizes sensing nanoparticles of cerium oxide that respond visually to antioxidant compounds. Due to ease of use of these sensors, inexpensive materials, and short time requirement (~1 h), this lab is appropriate for primary, secondary, and undergraduate courses. The lab and lesson expose students to the fields of nanotechnology, analytical chemistry, antioxidant chemistry, and antioxidant characteristics of botanicals and food constituents.



KEYWORDS: *Analytical Chemistry, Elementary/Middle School Science, High School/Introductory Chemistry, First Year Undergraduate, Chemical Engineering, Demonstrations, Nanotechnology, Free Radicals, Interdisciplinary*

■ LAB SUMMARY

Antioxidant polyphenols are some of the major bioactive compounds that have received attention throughout the past decade.[1] With current advances in nanotechnology, we have created low cost paper-based sensors[2] for detection of various analytes including antioxidants.[3] Metal oxide nanoparticles can be used as colorimetric inorganic indicators for antioxidants.[2−4] The laboratory presented herein describes an interactive investigation of paper sensors based on nanoparticle chemistry for the detection of polyphenols. The assay utilizes nanosized particles of cerium(IV) oxide, also known as nanoceria, immobilized on the surface of filter paper.[3] The immobilized nanoceria exhibits optical changes when in contact with antioxidants due to formation of charge transfer complexes.[2−4]

These changes are used to monitor antioxidant content of various samples. The sensors are easy to fabricate, low cost, and adaptable for use in a variety of settings. This is a task appropriate for undergraduate and high school students, as an introduction to field portable monitoring devices. The lab has been adapted as an introduction to nanoparticle science and paper sensors for elementary students, wherein they test various beverages and compare colorimetric readouts.

This laboratory provides a hands-on experience, wherein students in higher grades can make their own paper sensors. These sensors are hand-held, are portable, and require no use of advanced instrumentation. Students can visually observe the chemical reaction due to the strongly visible color changes accompanying the reaction of polyphenols with the immobilized particles. Students are exposed to redox chemistry during the discussion of free radicals and antioxidants. To analyze samples, secondary and undergraduate chemistry students create solutions containing antioxidants, make dilutions, and utilize multichannel pipettes. To analyze sensor response, students learn basic operations of Excel, or similar spreadsheet programs. They create and utilize calibration curves and, in the process, gain a working knowledge of creating graphs, calculating averages, standard deviations, logarithm calculations, and stoichiometric calculations. Exposure to this broad range of topics ties this lab experiment into various fields including basic laboratory skills, free radical/antioxidant and redox chemistry, nanoparticle science, portable sensor development, nutrition, mathematics, and computer use.

■ PEDAGOGICAL IMPACT

Paper assays are the least expensive alternatives to conventional measurement techniques.[5] Few such assays have been adapted for chemistry education.[6] The hands-on lab activity outlined here introduces students to nanoparticle-based paper assays for detection of antioxidants. This lab is unique from current educational laboratory activities related to antioxidant and

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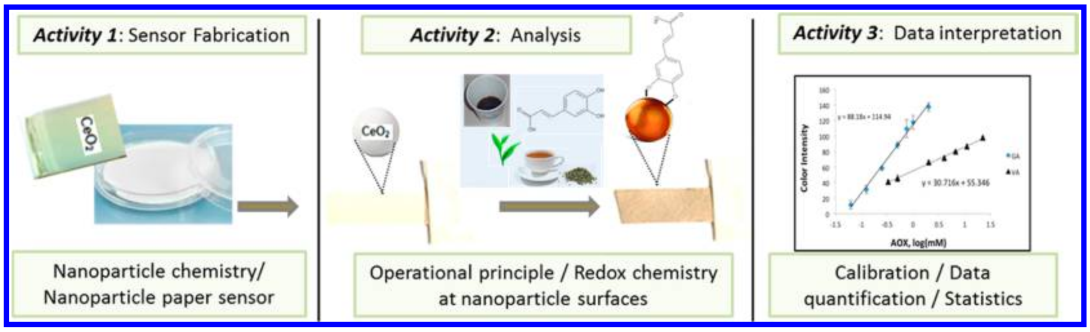

Figure 1. Experiment overview showing the sequence of laboratory activities and learning outcomes. Binding of caffeic acid (as an example of antioxidant) is shown in the middle schematic to illustrate the detection mechanism.

antioxidant assays. The assay is hands on, inexpensive, and easy-to-use, making it appealing to students ranging from elementary through college level science, food, and chemistry classes. It gives immediate feedback in the form of colorimetric response, motivating students and providing the ability to qualitatively analyze a sample with the naked eye and their own device. The paper-based assay is very inexpensive as compared to currently used antioxidant procedures (UV−vis,[7] NMR,[8] HPLC,[9,10] electrochemical square wave voltammetry[11]), making it financially appealing to school districts. Currently available laboratory experiments involving antioxidant detection include the popular UV−vis based DPPH assay,[7] NMR for investigative studies of an antioxidant additive,[8] HPLC and the spectroscopic TEAC assay to discuss the effects of processing on antioxidants,[9] HPLC and UV−vis to analyze presence and activity of rosmarinic acid,[10] and voltammetry to detect antioxidants in oils.[11] These experiments require specialized instrumentation for data acquisition and analysis. The portable method described here provides a low cost alternative that may make these types of experiments more widely available to schools without extensive funding.

■ EQUIPMENT AND REAGENTS

Cerium(IV) oxide (aq) nanoparticles can be purchased from Sigma-Aldrich. Filter paper for immobilization of particles can be purchased from Fisher Scientific (P5; medium porosity; 11 cm diameter). Antioxidant standards capsaicin (CP) and epigallocatechin gallate (EGCG) can be purchased from Sigma-Aldrich; ascorbic acid (AA) and gallic acid (GA) from Acros; quercetin (Q) from Alpha Aesar; and ellagic acid (EA) from TCI America. Antioxidant-containing samples can be attained from a wide variety of sources, as many teas and beverages contain significant levels of polyphenols. Beverages studied herein include Saranac beer, green tea, coffee, white grape juice, acai berry juice, orange juice, and apple juice, with water as a control.

■ HAZARDS

Nanoceria has been investigated for its therapeutic potential.[12] Its toxicity is under evaluation.[13] Widespread use of nanoparticles for industrial, medical, and research purposes is relatively new in recent decades, leaving the long-term effects of nanoparticle exposure largely unknown. The use of personal protective equipment including laboratory coats, gloves, and goggles is required throughout the experiment.

■ EXPERIMENT OVERVIEW

This experiment was devised with various levels of complexity and can be implemented for K−12 students as well as for chemistry-based college level STEM courses including general chemistry, food chemistry, analytical chemistry, and chemical engineering. Students can create their own sensors within an hour.[3,14] The procedure involves dipping the filter paper in 4% nanoceria dispersed in 0.5% acetic acid and allowing it to dry.[15]

At the undergraduate level, as a prelaboratory assignment, students should be expected to carry out a literature review, allowing them to investigate the role of antioxidants in human health, as well as methods used for their detection. The instructor should give a general introduction about redox chemistry and nanoparticle technology. Specifically, nanoceria must be introduced and discussed with regard to its redox properties and the interaction of these particles with antioxidants.[3] Several educational materials related to nanotechnology have been reported and can be used.[16] Students should be encouraged to use critical thinking to discuss antioxidants and free radicals and their role in human health, as well as which dietary sources contain them. Following this introduction, students should have a basic understanding of the purpose of creating such sensors, and what they can be used for.

Figure 1 presents the proposed sequence of the laboratory experiment including sensor preparation, analysis, and data interpretation. Considering the large number of samples and data set that can be analyzed in a short time, this exercise could be expanded to introduce statistics, e.g., analysis of variance (ANOVA), to determine similarities and differences within large sets of antioxidant-containing samples. Food chemistry students can also use the assay to study the antioxidant content of a variety of food products.

■ EXPERIMENTAL DETAILS

Background

Cerium oxide nanoparticles or nanoceria has two oxidation states, Ce(3+/4+).[2] The mechanism leading to the determination of antioxidants involves surface oxidation of nanoceria by antioxidants followed by formation of charge transfer complexes (Figure 1).[3] Alteration of the spectral properties at the particle surface can be monitored visually, as a color change from yellow to red/orange. Such changes are concentration dependent, allowing for quantitative monitoring of antioxidants. Analysis is a single step process consisting of addition of the sample on the sensor strip.

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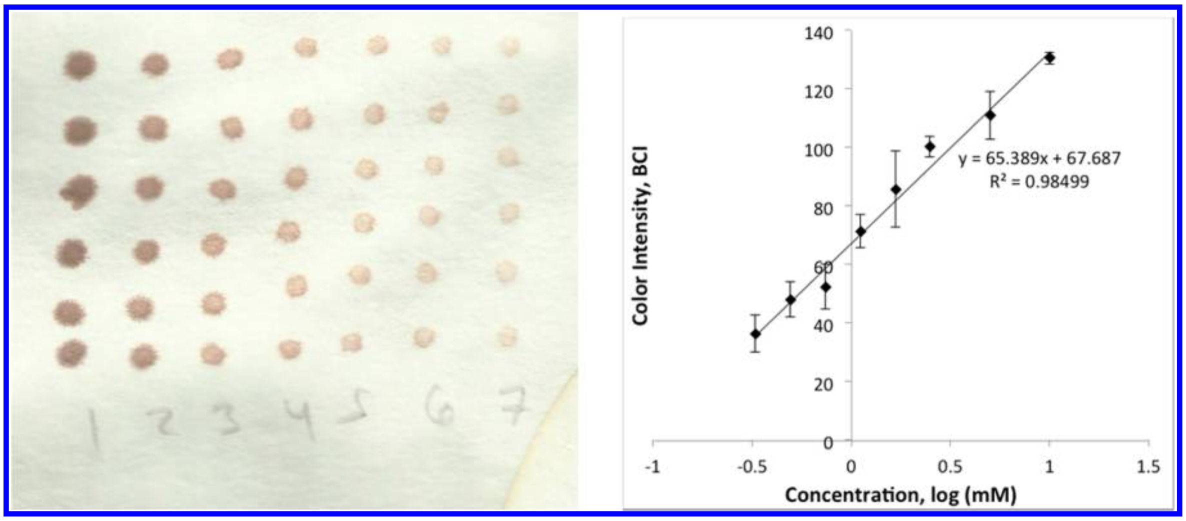

Figure 2. Visualization of a standard calibration curve using the NanoCerac Assay.

Evaluation of the Antioxidant Activity Using the Nanoceria Reducing Antioxidant Capacity (NanoCerac) Assay

Nanoceria sensors for antioxidant analysis, sensors must first be fabricated. These can be prepared by the instructor ahead of time, or by students if time allows. Creation of sensors by students allows them to witness their simplicity and accessibility, and emphasizes the user-friendly aspect of the assay. When sensors are ready, students can begin learning about and creating antioxidant calibration curves using their sensors. Students must first create a standard calibration curve for gallic acid (GA), which is used as a reference standard for antioxidant activity. To do this, students fill the first 6 rows of column 1 on a 96-well plate with 10 mM GA, and then create 1:3 serial dilutions in water using a multichannel pipet to transfer 150 μL of sample into 50 μL of water, in replicates of six, to ultimately fill the first 6 rows of columns 1−12. Using a multichannel pipet, students will then deposit six replicates (sample volume 2.5 μL) of each concentration, from low to high concentration onto 11 cm diameter nanoceria sensing sheets. These points will be analyzed for color and then used to create a BCI vs log (mM) calibration curve, the slope of which indicates antioxidant activity.

Data Quantification Using the Portable NanoCerac Assay, Achieved through Color Analysis

Students scan their sensors using a conventional office scanner, and analyze the red, green, blue (RGB) color breakdown using a tool such as Color Picker for PC or the Digital Color Meter for Mac. Blue has been found to be the most sensitive color channel for the color gamut seen here, and thus students will create calibration curves using the inverse of blue color intensity (BCI), which is on a scale of 0 (black) to 255 (white). Using Excel to create a graph, students will use BCI as the y-axis, and the log of the concentration (mM) as the x-axis. Each point will represent the average of six replicates, and students can create error bars by calculating the standard deviation of the replicates. This is an advantageous tutorial on Excel for students ranging from middle school to undergraduate levels, as they learn to arrange a data sheet using formulas to input and calculate the following: GA concentrations, inverse and averages of color intensities, log of concentrations, and standard deviations of values. They also have the opportunity to practice creating a proper scatter plot, adding a trend line, understanding correlation coefficients, and labeling the graph with axis names, a title, and a legend. Figure 2 depicts a GA calibration curve using this method. As indicated in the procedure, all 12 rows of a 96-well plate were filled with sample and deposited on paper, but the linear range for each antioxidant solution differs. Each sensing sheet can hold seven dilutions, with six replicates. Dilutions 1−7 are shown in Figure 2 as a visual example of how the color appears, and what the sample size looks like on the sensing paper, when applied in replicates of six.

The reproducibility of this assay is excellent. Students will find a relative intra-assay standard deviation (RSD) of the slope of a BCI vs log (mM) calibration curve to be less than 10%. In a trial done at Italy's national nutritional research institute, INRAN, the intra-assay RSD was 8 ± 4%, where six replicates were done for each point constituting one assay; and 27 separate assays were compared to one another. Interassay RSD was found to be 7 ± 3%, where the assay was performed three times; and this process was done nine times. Multiple batches of sensors were also compared to one another, to find a RSD of 4 ± 3%, and three different brands of filter paper (Fisher, Spectrum, and one unknown brand) were also compared to find a RSD of 8 ± 3%. Considering its high reproducibility, this assay could be used as an introductory statistics exercise, wherein students can compare their experimental outcomes to others' in the class, to determine accuracy and reproducibility of the assay.

■ RESULTS AND DISCUSSION

Sample Analysis

Once the standard curve has been established, students can analyze various samples in the same manner and compare the slope of the resulting calibration curve to that of their antioxidant standard, GA, to determine antioxidant activity. The formula used for this is $slope_{sample}/slope_{GA}$ = mM GA with equal activity to 1 mM sample (or mM GA equivalents (GAE)).[3] For their first sample, students can begin by analyzing a pure compound such as ascorbic acid (vitamin C) or resveratrol to determine the activity of another antioxidant relative to their GA standard. Figure 3 shows a calibration curve of ascorbic acid created using the same method. Using slope comparison, the antioxidant activity is 0.3 mM GAE.

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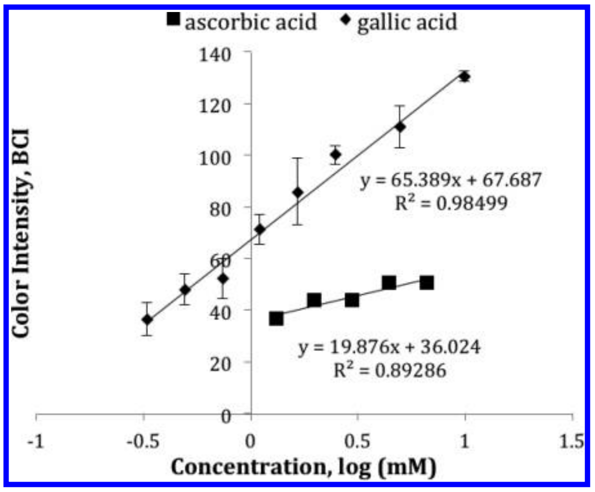

Figure 3. Calibration curve of vitamin C, or ascorbic acid (AA), showing a shorter linear range than gallic acid (1 to 7 mM) and a less steep slope (19.876 BCI units/log(mM)), creating a GAE of 0.3 mM, or about one-third the antioxidant activity of gallic acid.

For practice interpolating values into a calibration curve to determine concentration, students can recreate a quality control testing process in the classroom. Herein, students would dissolve a vitamin C or resveratrol supplement into water or ethanol, and deposit the sample onto nanoceria sensors at a dilution that would create a BCI that falls within the linear range of the standard curve. The resulting color intensity could be interpolated into the equation for the line, and the concentration in solution and the original tablet can be identified in terms of mM and then milligrams. Students can then compare their value to that reported. Using molecular weight, students can practice stoichiometric calculations to determine the milligrams of active ingredient in the supplement. This activity acts as a valuable introduction to calibration curves, stoichiometric calculations, dilutions, and quality control, which are all essential knowledge and practical skills in all fields of chemical analysis. This experiment can be paired with conventional analytical assays for the detection of antioxidants including the ABTS assay, the ORAC assay, Folin Ciocalteu reagent assays or HPLC.[9] Students can discuss the detection principles of the various assays and compare the results, including advantages and limitations of each method.

Aside from analysis of pure antioxidant solutions, students can analyze the antioxidant activity of more complex solutions such as beverages and plant extractions. For example, Saranac beer has been analyzed by undergraduate students, who found an activity of 0.57 GAE. Tea is another good example of an antioxidant-containing beverage that is easily analyzed using the NanoCerac sensors. Twenty-four varieties of commercial green tea were analyzed by the authors in a previous study[17] which employed this method. Antioxidant activity values ranged from 0.52 to 0.92 mmol gallic acid equivalents (GAE) per gram tea, and showed an average value of 0.73 mmol GAE/g tea, with a coefficient of variance of 15%. The NanoCerac assay can be used as a high-throughput method for rapid analysis of antioxidant activity of a large number of samples. This approach could be particularly appealing for food chemistry classes as a method to screen a variety of food samples for their antioxidant activity, comparing, for example, fruit juices from different sources. The method can be paired with automated color analysis, created using a MatLab program or using a portable color reader device such as the Pantone, to facilitate rapid color reading of multiple color strips, as was done in our study of green teas.[17]

In more advanced classes, students can design an array of multiple sensors, each consisting of a different metal oxide nanoparticle to analyze complex mixtures found in real samples for their primary acting component. This array can identify and quantify the primary polyphenol contained in a real sample through systematic color matching of unique colorimetric responses of each polyphenol on each metal oxide.[17] This method is outlined in the Supporting Information.

■ IMPLEMENTATION AND EVALUATION

This experiment was implemented with five undergraduate students during independent study and research in our laboratory. Their work was supervised by the author, who found that undergraduate students were able to quickly master the processes required for development of calibration curves (sensor fabrication, creation of an antioxidant solution, preparation of serial dilutions, deposition of samples onto sensors, analysis of colors, and input and analysis of data using Excel). With guidance, these undergraduates were able to create calibration curves independently with minimal scaffolding or teacher support. These results indicate that the undergraduate students in a chemistry-based laboratory should also do well with this experimental procedure.

■ EVALUATION IN AN ELEMENTARY SCHOOL

The above information is intended for instruction of high school and college level students. However, these sensors can also be used for experiments implemented in lower levels, including elementary and middle school science classes. One such lesson was implemented to an elementary school. Elementary aged students were taught about antioxidants in relation to health and human consumption using a PowerPoint presentation (available upon request) and group discussion. They participated in a hands-on, group participatory demonstration of free radical and antioxidant chemistry, outlined in the Supporting Information, which allowed students a chance to visualize reactions as they may take place in the body. Students then got into groups for their lab exercise and were given preprepared sensing sheets. Each group tested various beverages by dipping sensors in solutions. Sensors were prefabricated with handles on them so students would not touch the sensing strip. After sampling, students wrote the sample name on the white handle, for easy analysis. Each group then compared the color intensity of each sample and ranked beverages in order of strongest to weakest hypothesized antioxidant activity.

Table 1 displays the results attained from four elementary classes, wherein students ranked beverages by relative antioxidant capacity based on color intensity of sensor response. All four classes successfully ranked beverages in the same order, attesting to the reproducibility and reliability of assay outcomes. Students ranked beverages in the order acai berry juice, coffee, green tea, orange juice, and apple juice, representing samples with high to low antioxidant activity.

Evaluation

When this lesson was executed in four elementary classrooms, with class sizes ranging from 14 to 23 students, prelesson and postlesson quizzes were administered. Questions addressed information including the definitions of antioxidants, free

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Table 1. Laboratory Results for Two Mixed Elementary Classes and Two Fifth Grade Classes[a]

	Beverage Ranking Grade 4-6 Class 1	Beverage Ranking Grade 4-6 Class 2	Beverage Ranking 5th Grade Class 1	Beverage Ranking 5th Grade Class 2	Color Response
1	Acai	Acai	Acai	Acai	
2	Coffee	Coffee	Coffee	Coffee	
3	Green Tea	Green Tea	Green Tea	Green Tea	
4	OJ	OJ	OJ	OJ	
5	AJ	AJ	AJ	AJ	

[a]Students were asked to rank five antioxidant-containing solutions by relative antioxidant content based on the colorimetric response formed on cerium oxide sensing papers.

radicals, and oxidative stress, the role of antioxidants in the body, and where they can be found. More students answered each question correctly on the postlesson quiz than on the prelesson quiz (Figure 4), in both the after-school-care program (grades 4−6) and the fifth grade classroom. This indicates that all students gained knowledge throughout the course of the class period. The fifth grade group scored slightly higher on the prelesson quiz than the after-school-care group, demonstrating more advanced deductive reasoning skills, or possibly some prior knowledge on the subject. Higher fifth grade prelesson scores could also be representative of the presence of younger students in the after-school-care program, or it could be indicative of the level of focus achieved in the classroom during the school day as compared to during activities provided at their after-school-care program.

Table 2 evaluates student opinion of the lab regarding whether they found it relevant to their daily life, if they felt they learned from the lab, and if they felt it would affect their dietary choices, among other things. Overall, the response was good, with the average ratings of the lab being 4 out of 5, with 5 being excellent and 0 representing a bad experience. Individual student comments can be found in the Supporting Information. Comments indicate the following: (1) students felt they learned about foods that could be healthy for them, (2) students enjoyed using the sensing strips, and (3) students thought the interactive part of the lesson was most fun.

Table 2. Results of the Questionnaire Given to Each Student Following the Experiment[a]

Question	Average
Rate this experiment.	4.3 ± 1.1
Rate how interesting you found this experiment.	4.1 ± 0.9
Rate the effectiveness of this experiment for helping you understand antioxidants.	4.2 ± 1.4
Rate how well does this experiment related to your daily life.	3.4 ± 0.8
Rate how effective this experiment was at changing the way you make future food and drink choices.	3.9 ± 0.9

[a]Students ranked their experience from on a number scale of 0−5 with 5 being the best.

CONCLUSION

This laboratory provides students with an opportunity to learn about the unique physicochemical and optical properties of nanoceria particles and their interaction with antioxidant compounds. Through hands-on activities, students fabricate their own measuring device based on the nanoceria chemistry and discover that these particles can be used as a colorimetric indicator of the antioxidant activity of a food sample. The many unique features of the assay, including portability and low cost, give students of all ages an opportunity to explore antioxidants with respect to their chemical properties, the reactions they undergo, their natural sources, and how to identify them in real samples. Students enjoyed using the device to test various types

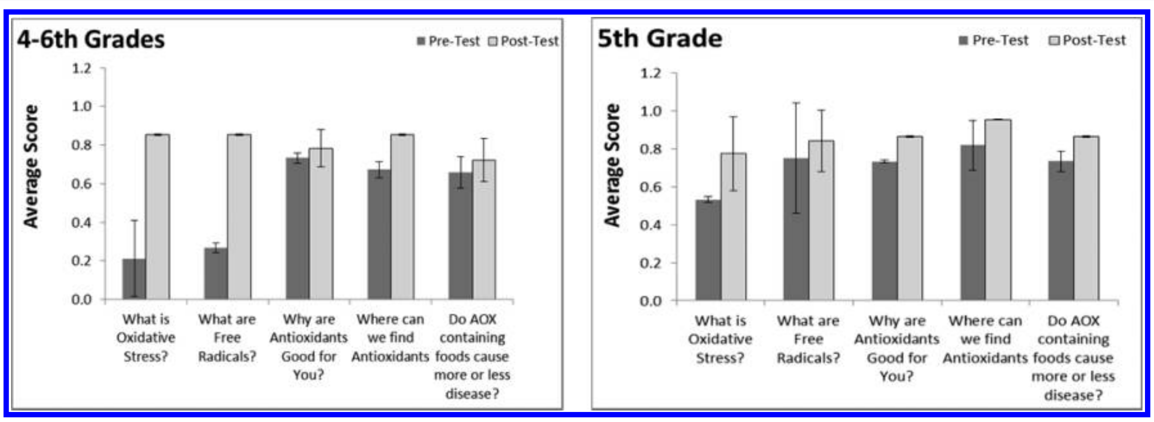

Figure 4. Results of prelesson quiz and postlab quiz for four classes: two "3 O'clock Block" after-school-care groups (grades 4−6) and two 5th grade classes; all from the same school district, Brasher Falls, New York. Error bars represent standard deviation from averages found by comparing scores from two sections of the same class. Each section contained between 14 and 23 students.

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of drinks for their antioxidant content, as is reflected in their comments summarized in the Supporting Information. This experiment can be extended to design various types of paper-based analytical devices for analysis of other target analytes including glucose, enzymes (e.g., alkaline phosphatase), and phenolic compounds.[2,4,18]

■ ASSOCIATED CONTENT

Supporting Information

All necessary handouts for the instructor (quiz and experiment evaluation), as well as instructional materials (instructions and script for the group activity). A description of how this lab can be modified for identification of sample composition, with descriptive figures to facilitate explanation. This material is available via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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