

# A smartphone colorimetric reader integrated with an ambient light sensor and a 3D printed attachment for on-site detection of zearalenone

Yuan Chen<sup>1</sup> · Qiangqiang Fu<sup>1</sup> · Dagang Li<sup>2</sup> · Jun Xie<sup>1</sup> · Dongxu Ke<sup>3</sup> · Qifang Song<sup>1</sup> · Yong Tang<sup>1</sup> · Hong Wang<sup>1</sup>

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**Abstract** Smartphone biosensors could be cost-effective, portable instruments to be used for the readout of liquid colorimetric assays. However, current reported smartphone colorimetric readers have relied on photos of liquid assays captured using a camera, and then analyzed using software programs. This approach results in a relatively low accuracy and low generality. In this work, we reported a novel smartphone colorimetric reader that has been integrated with an ambient light sensor and a 3D printed attachment for the readout of liquid colorimetric assays. The portable and low-cost (\$0.15) reader utilized a simplified electronic and light path design. Furthermore, our reported smartphone colorimetric reader can be compatible with different smartphones. As a proof of principle, the utility of this device was demonstrated using it in conjunction with an enzyme-linked immunosorbent assay to detect zearalenone. Results were consistent with those obtained using a professional microplate reader. The developed

smartphone colorimetric reader was capable of providing scalable, cost-effective, and accurate results for liquid colorimetric assays that related to clinical diagnoses, environment pollution, and food testing.

**Keywords** Smartphone · Zearalenone · Enzyme-linked immunosorbent assays · Colorimetric reader · Ambient light sensor

## Introduction

In modern society, a series of technologies have been developed and improved upon in regards to the diagnosing and prevention of disease [1–3]. Beyond the field of clinical diagnoses, convenient, fast, and efficient methods were also needed for the detection of increasingly serious environmental pollutants and food safety issues [3–5]. Liquid colorimetric assays have been commonly used due to their high stability, low cost, and high specificity [6]. The application of this method has been used for decades for the detection of glutamic pyruvic transaminase [7], creatinine [8, 9], organophosphorus pesticides [10, 11], and hydrogen peroxide. [12] Currently, ELISA kits and biochemical analysis kits comprised a large share of the tools used for clinical diagnoses, food safety, and environment pollution. Additionally, various liquid colorimetric assays have been developed, including aptamer-based biosensors [13–15], DNAzyme-based assays [16, 17], and nanomaterial-based biosensors [18–20]. However, current liquid colorimetric assays mainly require a laboratory-based infrastructure whereas their utility would be greatly increased by point-of-use deployment.

Smartphone biosensors would be cost-effective and handheld tools for liquid colorimetric assay readout [21, 22]. A smartphone could wirelessly integrate with the Internet and

Y.C., Q.F., and D.L. contributed equally to this work.

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✉ Yong Tang  
tyjaq7926@163.com

✉ Hong Wang  
wanghong@jnu.edu.cn

- <sup>1</sup> College of Life Science and technology, Jinan University, No. 601, Huangpu Avenue, Guangzhou 510632, China
- <sup>2</sup> Institute of Animal Science Guangdong Academic of Agricultural Sciences, Guangzhou, Guangdong 510632, China
- <sup>3</sup> School of Mechanical and Materials Engineering, Washington State University, 355 NE Spokane Street, Pullman, Washington 99164, USA

act as a unique platform for the development of various low-cost, easy operation, and handheld instruments. Currently, permanent physical sensors in smartphones, such as the digital camera [23, 24], wireless device [25, 26], USB port [27], and audio jack [28], in combination, have been used to fabricate biosensors. Smartphones played important roles in microscopy [29], cytometry [30], colorimetric assay readers [31], surface plasmon resonance imaging [32], spectrometers [33], electrochemical workstation [34], and lateral flow assay readers [35]. For the readout of an ELISA kit, or other liquid colorimetric assays, various smartphone platforms were developed. A microchip ELISA, first reported in 2011 [36], employed a portable cell phone to quantify an ovarian cancer biomarker in urine. The processing of microchip ELISA results was done using the customized software MATLAB, which calculated the red (R) pixel values of the TMB (3, 3', 5, 5'-tetramethylbenzidine) substrate. However, these methods were not handheld and the sensitivity was shown to decrease for wells that were closer to the edges of the multi-well plate. To overcome this problem, the Aydogan Ozcan group [37] developed a new approach for ELISA kit analysis that relied on using an array of 96 individual optical fibers that has collected transmitted light from a 96-well plate and then calculated the concentration of the target by analyzing the blue channel pixel intensities of the TMB substrate. These techniques were believed to have great potential for the real-time readout ELISA kit. For the precise quantification of ELISA kits and other liquid assays, many calibration methods such as black box, paralleled detection, and a mapping algorithm were developed [38–40]. However, up until now, the imaging capabilities of a smart phone were not precise, and the simple image capture and pixel analysis meant that precise quantification was also difficult [21, 41]. To solve this problem, our group developed a new approach that used an ambient light sensor in smartphones to measure transmitted light intensities of a liquid assay [42, 43]. Compared to the above colorimetric methods, this spectrophotometric approach was more precise. Unlike smartphone camera-based colorimetric liquid assay readout methods that required a specific distance between the camera and liquid assay to adjust the focal length of the camera, our reported attachment directly attached to the ambient light sensor and then measured the transmitted light intensity of the liquid assay. This approach utilized a simplified structure and reduced the volume of required attachments. However, with our reported attachment, only one sample can be measured at a time and when multiple samples require detection, it is labor intensive and time consuming.

Here, we developed a cost-effective and handheld smartphone colorimetric reader for the rapid multichannel monitoring of an ELISA. The smartphone colorimetric reader is composed of a smartphone equipped with a custom-designed accessory that was made using a low-cost desktop 3D printer. The design provided a significantly more compact

and multiple sample detection platform. This device was validated by using it to monitor the mycotoxin zearalenone (ZEN), a metabolite produced by several species of *Fusarium* fungi, such as *Fusarium graminearum* and *Fusarium culmorum*, by ELISA. We believe the device, designed to read ELISA kit, could easily be applied to other approved liquid colorimetric assay kits related to environmental monitoring, clinical diagnoses, and food testing.

## Materials and methods

### Materials

The commercial microwells were purchased from JET BIOFIL. Anti-ZEN monoclonal antibodies (mAbs) and the coating antigen ZEN-BSA (bovine serum albumin) were prepared by our laboratory [44]. LEDs (450 nm, 525 nm, 610 nm, and 680 nm) were purchased from Shenzhen OCTAI Co., Ltd. Goat anti-mouse IgG-horseradish peroxidase conjugate was purchased from Sigma-Aldrich (St. Louis, MO, USA). The battery (1.5 V) was purchased from VSAI. Non-fat milk powder, resistors, and switch wires were purchased from a local store. TMB substrate was purchased from Xiya reagent (Guangzhou, China). The absorbance of the liquid assays was analyzed using a Synergy H1 Hybrid Multi-mode Microplate Reader (Bio-Tek Instruments, Inc.). A 3D printer was purchased from the SHINING 3D (Hangzhou, China). The material used for the fabrication of the device was polylactic acid. Preparations of gold nanoparticles, gold nano-flowers, and triangular silver nanoprisms were referred from previous works [45–47]. In our design, the HUAWEI Honor 6 was chosen as the basic smartphone to be used in our development of a smartphone colorimetric reader.

### Design of the smartphone colorimetric reader

The smartphone colorimetric reader was for the ELISA kit, the emission lights were 450 nm, and the resistance of the resistors was 10,000  $\Omega$ . The design chart of device was drawn by a software (Solidworks 2014) and then processed by the printer's own software, 3Dstar.

### Smartphone colorimetric reader for readout of ZEN ELISA kit

The ELISA for ZEN detection was performed using an indirect competitive ELISA protocol format. Typically usually, polystyrene microwells were coated with 100  $\mu$ L per well of ZEN-BSA in 50 mM coating buffer and incubated overnight at room temperature. The coated microwells were then washed three times with PBST (phosphate buffer, NaCl 137 mmol/L, KCl 2.7 mmol/L, Na<sub>2</sub>HPO<sub>4</sub> 4.3 mmol/L,

$\text{KH}_2\text{PO}_4$  1.4 mmol/L, pH 7.4, 0.05% Tween 20) buffer and then 200  $\mu\text{L}$  of 1% BSA was added in order to block the surface of each microwell and incubated at 37 °C for 2 h. The coated microwells were washed three times with washing buffer and then stored at - 20 °C for future use.

To construct the calibration curve for the ZEN ELISA, 50  $\mu\text{L}$  of an anti-ZEN mAb (50 ng/mL) in PBS (NaCl 137 mmol/L, KCl 2.7 mmol/L,  $\text{Na}_2\text{HPO}_4$  4.3 mmol/L,  $\text{KH}_2\text{PO}_4$  1.4 mmol/L, pH 7.4) buffer and 50  $\mu\text{L}$  of different concentrations of a ZEN standard (0 ng/mL, 1.56 ng/mL, 3.13 ng/mL, 6.25 ng/mL, 12.5 ng/mL, 25 ng/mL, 50 ng/mL, and 100 ng/mL) solutions were mixed and added into microwells. After 45 min, unbound mAbs were removed by washing three times with PBST buffer. Then, 100  $\mu\text{L}$  of PBST buffer with a diluted goat anti-mouse IgG-horseradish peroxidase conjugate (100 ng/mL) was added to each microwell and incubated at 37 °C for 30 min. Each microwell was washed with PBST buffer five times and then 100  $\mu\text{L}$  of the TMB substrate was added and incubated for 10 min, after which 50  $\mu\text{L}$  of stop solution was added to each microwell to terminate the reactions. Transmitted light intensities and absorbance of TMB substrate were measured using the smartphone colorimetric reader and a professional microplate reader.

### Specificity of the ELISA for ZEN detection

To evaluate the specificity of the ELISA kit for ZEN detection, 50  $\mu\text{L}$  of a 50 ng/mL solution of the mycotoxins (zearalenone,  $\alpha$ -zearalenol,  $\beta$ -zearalenol,  $\alpha$ -zearalanol,  $\beta$ -zearalanol) were tested. The ELISA protocols followed for the detection of these mycotoxins were similar to the one followed for ZEN detection.

### Analysis of ZEN corn flour samples

Analysis of ZEN in corn flour samples was referred from a previous study [48]. Corn flour samples (10 g) were extracted with 50 mL of 70% (v/v) methanol and 4% (v/w) NaCl with shaking of 3 min, and then spiked with different concentrations of ZEN. The sample solution was centrifuged at 2000 rpm and the supernatant was diluted to five times its volume using PBS buffer for the ELISA (see Electronic Supplementary Material (ESM) Fig. S1).

## Results and discussion

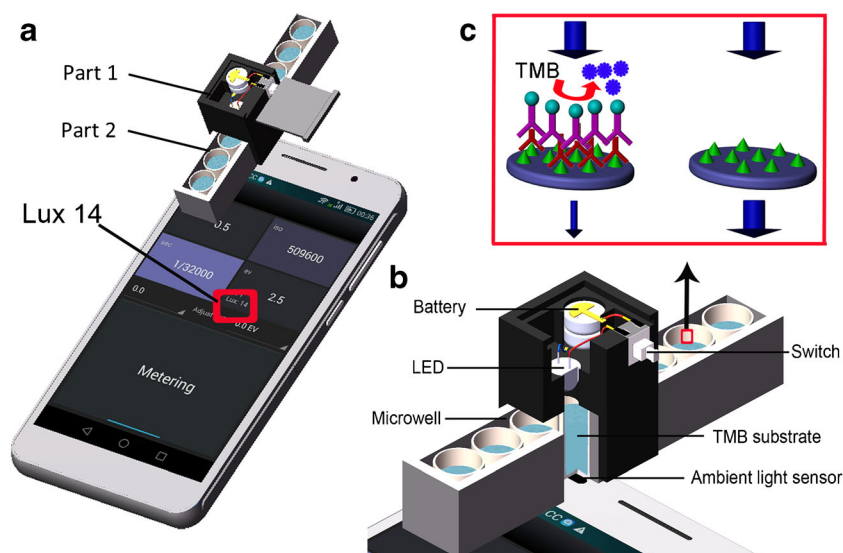
### 3D printed attachment of smartphone colorimetric reader

In smartphones, the ambient light sensor is a default configuration used for automatically adjusting the light intensity of the screen according to the ambient light. In this used smartphone, ambient light sensor was located on top of the screen. The 3D-

printed attachment of the smartphone colorimetric reader consists of two parts. Part 1 was a stable light source powered by two button cells (1.5 V) and its intensity was adjusted using a resistor. These electronic components were assembled into a 3D-printed plastic host (20 mm  $\times$  25 mm  $\times$  17 mm) and connected by conductive wires. Part 2 (76 mm  $\times$  13 mm  $\times$  12 mm) was applied to a hosting microplate. Once the ELISA was completed by the operator, the microwell was assembled into part 2, as shown Fig. 1a. After part 2 being connected to part 1, the cartridge was then attached to the ambient light sensor of the smartphone, and the LED was aligned with the ambient light sensor. When the switch was turned on, the light emitted from the LED was transmitted across the liquid colorimetric assay for the measurement. Each microwell could be read just by sliding part 2. Measured light intensity was presented on the screen of smartphones by a free Android application, Light Meter.

### Characterization of smartphone colorimetric reader

The stability of smartphone colorimetric reader was analyzed using a TMB substrate that was catalyzed by HRP and then diluted down to a number of different concentrations. The transmitted light intensity of the same batch of TMB substrate catalyzed by HRP was measured five times. No differences were found among the measurements of each replicate (Fig. 2a), indicating that the developed smartphone colorimetric reader was highly stable. Due to pixel and focal length differences among various smartphone brands, it was likely that the accessories required for current reported camera-based smartphone colorimetric readers may not be able to be used on other smartphone brands. In this study, the transmitted light intensity of the TMB substrate was measured. Despite differences in the measured transmitted light intensities from different smartphone brands, the ratio of the measured transmitted light intensities of two concentrations TMB substrate was equal (Fig. 2b). Therefore, the developed smartphone colorimetric reader could be run on different smartphones simply by calibrating the software parameters or the setting controls. Absorption spectra of commonly used liquid colorimetric assays probably range from violet light to red light. To confirm the extensive applicability of our developed smartphone-based colorimetric reader, the transmitted light intensities of an ELISA of the TMB substrate (maximum absorption spectra at 450 nm), gold nanoparticles (maximum absorption spectra at 525 nm), gold nano-flowers (maximum absorption spectra at 610 nm), and triangular silver nanoprisms (maximum absorption spectra at 680 nm) were measured by the smartphone-based colorimetric reader. The transmitted light intensities of these liquids were measured. Also, the emitted light of the used LEDs were chosen to match the maximum absorption spectrum of the liquids. Compared to the control group (microwells not containing liquid), the transmitted light



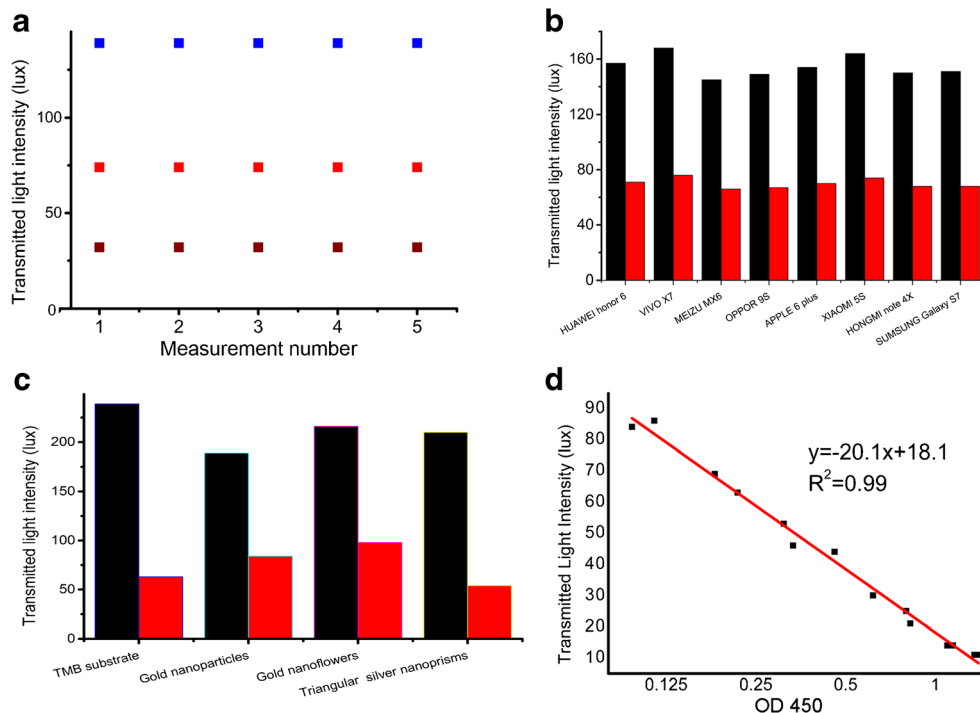
**Fig. 1** Mechanism of smartphone colorimetric reader. (a) Schematic of the 3D-printed optical attachment. Measured transmitted light intensity was displayed on a screen of the smartphone. In the square frame, there is a photograph of the actual smartphone-based colorimetric reader running on a smartphone. (b) The principle of the ELISA detection by the

smartphone. (c) The principle of the ELISA detection of ZEN contents. When the ZEN concentration was low, low intensity of transmitted light was measured. When the ZEN concentration was high, high intensity of transmitted light was measured

intensities of these liquids were significantly decreased (Fig. 2c), which implied that the smartphone colorimetric reader could read out a series of liquid colorimetric assays. For current smartphones, the ambient light sensor can respond to light from 340 to 680 nm, which means that the developed smartphone-based colorimetric reader can read results of

different assays with maximum absorption wavelengths between 340 and 680 nm. Transmitted light intensity and absorbance value of diluted TMB substrates were measured by both the smartphone colorimetric reader and a professional microplate reader. Results obtained from these devices were fitted and showed a 99% correlation (Fig. 2d), indicating that the

**Fig. 2** Characterization of the smartphone colorimetric reader. (a) Stability of smartphone colorimetric reader. (b) Universality of the smartphone colorimetric reader for different smartphones. (c) Smartphone colorimetric reader reads transmitted light intensity of different materials. (d) The linear correlation between the smartphone colorimetric reader and the professional microplate reader





developed smartphone colorimetric reader was a very accurate tool to read liquid colorimetric assays.

### Readout of ELISA for the detection of ZEN by the smartphone colorimetric reader

To validate the application of developed smartphone colorimetric reader, we prepared an ELISA kit to detect ZEN and read by the smartphone colorimetric reader. ZEN was a metabolite produced by several species of *Fusarium* fungi, *F. graminearum* and *F. culmorum* in particular. ZEN was also the most common mycotoxin found in food and feed, and there has been an increasing awareness of the hazards posed to humans by its presence in both food and feed [49]. ZEN contaminations may occur throughout the entire process of agro-food production, including field cultivation and storage. In both human and animals, the ingestion of ZEN-contaminated food or feed can lead to acute intoxication, reduced weight gain, immunosuppression, and an increased risk of cancer [50, 51]. Therefore, most countries have set strict limits on the levels of ZEN in food or feed. For China, Australia, Ukraine, and Japan, the maximum permissible level of ZEN in feed or food is set at 500, 50, 40, and 20  $\mu\text{g}/\text{kg}$ , respectively, and for the European Union, guidance values of

0.1–2  $\text{mg}/\text{kg}$  in animal feed have been recommended under Commission Recommendation 2006/576/EC.

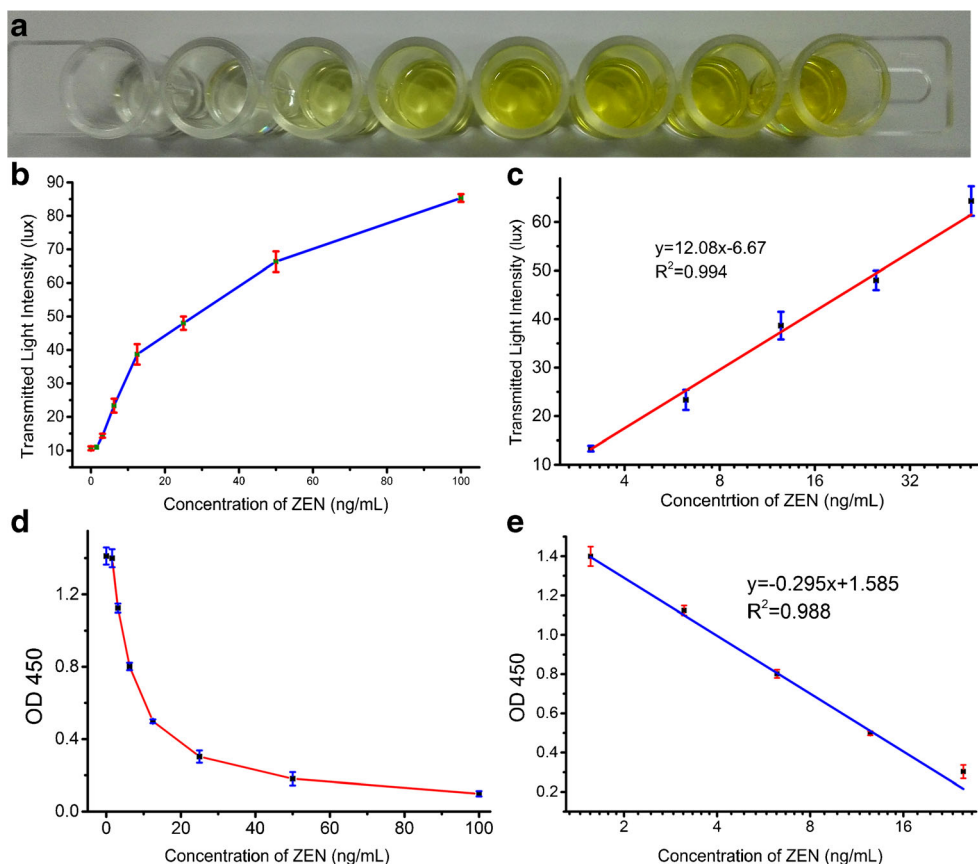
The detection of ZEN follows a competitive ELISA. As shown in Fig. 3a, the intensities of the measured transmitted light increased along with increasing concentrations of ZEN (Fig. 3b). The measured transmitted light intensity was used to determine the concentrations of ZEN. Results showed that the linear detection range of the ZEN ELISA kit was from 3.13 to 50  $\text{ng}/\text{mL}$  (Fig. 3c), and the limit of detection was 2.12  $\text{ng}/\text{mL}$ .

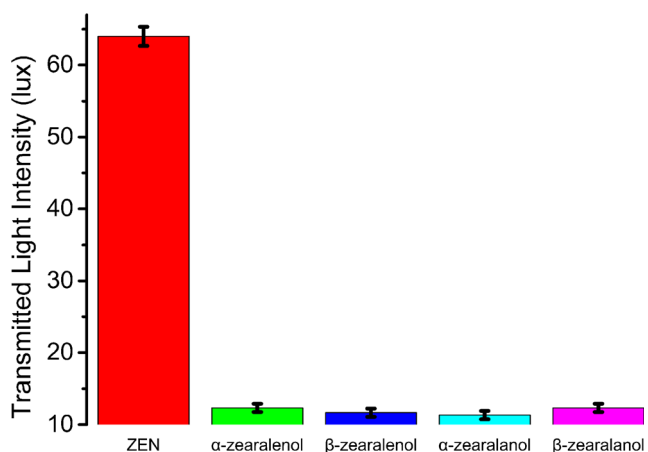
### Comparison of results obtained from smartphone colorimetric reader and reference microplate reader

To compare the results obtained from the smartphone colorimetric reader and a professional microplate reader, the ZEN ELISA was read by both devices simultaneously. The results from the professional microplate reader showed that the intensity of light decreased with increasing ZEN concentrations (Fig. 3d). The measured absorbance intensities were used to quantitatively analyze the concentrations of ZEN, which were calculated to be 1.56–25  $\text{ng}/\text{mL}$  (Fig. 3e). The limit of detection was 2.04  $\text{ng}/\text{mL}$ . Results of these devices were similar, indicating that the developed smartphone colorimetric reader could read ELISA kit for ZEN detection.

**Fig. 3** ELISA for ZEN detection.

(a) Photograph of ELISA for the detection of different concentrations of ZEN. (b) ZEN-concentration-dependent transmitted light intensity readouts using the smartphone-based colorimetric reader. (c) The calibrated curve of ELISAs for ZEN obtained by the smartphone colorimetric reader. (d) ZEN-concentration-dependent absorbance at 450 nm read using a professional microplate reader. (e) Calibrated curve of ZEN ELISA readout using a commercial microplate reader. X-axis of (c) and (e) is  $\log_2$  scale. Each value represents the mean of three independent experiments ( $n = 3$ )





**Fig. 4** Specificity of ZEN ELISA kit. Each value represents the mean of three independent experiments ( $n = 3$ )

### Specificity of ELISA for detecting ZEN

To analyze the specificity of the ELISA kit, definite concentration samples of analogues were tested by the ELISA kit and read by using the smartphone colorimetric reader. Obtained transmitted light intensity was recorded and then calculated a value using the calibrated curve of ZEN ELISA kit. The accurate cross-reaction rates of these analogues were calculated using the following relationship: value/used concentration  $\times 100\%$ . Considering that the antibodies we selected for ZEN were highly specific, 50 ng/mL of these analogues was selected. In this study, the measured transmitted light intensities for 50 ng/mL of  $\alpha$ -zearalenol,  $\beta$ -zearalenol,  $\alpha$ -zearalanol, and  $\beta$ -zearalanol were lower than 13 lx (Fig. 4), which was out of the linear detection range of the ZEN ELISA. This result indicated that the cross-reaction rate of developed ELISA was lower than 6.26%.

### Recovery of developed ELISA for ZEN detection in corn flour

Post-extracted corn flour was spiked with different concentrations ZEN and then analyzed by using an ELISA. Three

repeated measurements were performed at each concentration. The results were read by the smartphone colorimetric reader and showed high recoveries (83.6% to 89.68%) (Table 1). This result indicated that the developed smartphone colorimetric reader was a useful tool for the detection of ZEN in corn samples.

### Conclusions

In this study, we reported a smartphone colorimetric reader. Unlike previously reported liquid colorimetric readout platforms which used cameras, we utilized the ambient light sensor of a smartphone to measure transmitted light intensities of a liquid colorimetric substrate. This approach has the following advantages. (1) The accessories were directly attached to the ambient sensor and do not require a hood to adjusted the focus distance from the smartphone camera to liquid assay, therefore minimizing the size of the entire platform. (2) The developed reader used simplified light and electronic paths due to the fact that we directly applied ambient smartphone sensor to measure the transmitted light intensity of a liquid assay. The cost of the accessories was only about \$0.15. (3) The developed colorimetric reader could read the transmitted light intensities of different liquid assays via changes in LED light resources. (4) The developed smartphone-based colorimetric reader was compatible with different smartphones by simple calibration of software parameters or adjustments in setting controls. (5) This spectrophotometric approach was more accurate than previous image-analyzing-based approaches. This approach is useful as a point-of-use device so long as the colorimetric assay components are available as a complete kit without the need for a laboratory. Our novel smartphone colorimetric reader has the ability to provide scalable, cost-effective, and accurate results for numerous liquid colorimetric assays, including ELISA kits, biochemical assay kits, aptamer biosensors, DNAzyme-based sensors, and plasmonic nano-biosensor-related clinical diagnoses as well as environment pollution and food testing.

**Table 1** Recoveries of ELISA for ZEN in corn samples measured using a smartphone-based colorimetric reader

Spiked concentration (ng/mL)	Read by smartphone-based colorimetric reader (ng/mL) <sup>a</sup>	CV (100%) <sup>b</sup>	Recovery (100%) <sup>c</sup>	Read by professional microplate reader (ng/mL) <sup>a</sup>	Recovery (100%) <sup>c</sup>
20 ng/mL	17.65 $\pm$ 1.26	7.14	88.25	17.01 $\pm$ 1.12	85.05
15 ng/mL	13.51 $\pm$ 1.82	13.47	90.07	13.68 $\pm$ 1.58	91.2
10 ng/mL	9.33 $\pm$ 0.86	9.21	93.3	9.31 $\pm$ 0.52	93.1
5 ng/mL	4.18 $\pm$ 0.43	10.29	83.6	4.64 $\pm$ 0.33	92.8

<sup>a</sup> Results are expressed as the mean  $\pm$  SD ( $n = 3$ )

<sup>b</sup> Coefficient of variation (CV) and recovery are calculated using the following equation: CV = (SD/mean)  $\times 100\%$

<sup>c</sup> Recovery (%) = (detected concentration/spiked concentration)  $\times 100$

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

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