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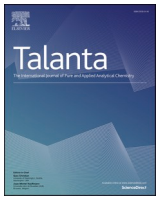

Recent advances and perspectives of enzyme-based optical biosensing for organophosphorus pesticides detection

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ABSTRACT

The overuse or abuse of organophosphorus pesticides (OPs) can bring about severe contamination problems in foodstuff and the environment, which will seriously threaten human health and the ecosystem's cycle. Hence, it is in high demand to establish sensitive, portable, specific, and cost-effective methods for monitoring OPs to control food safety, protect the ecosystem, and prevent disease. The optical biosensor with enzyme as bio-recognition elements has been an effective alternative for OPs detection. Herein, we firstly introduce various enzymes, sensing mechanisms, advantages and disadvantages used as bio-recognition elements in optical sensing for OPs detection. Then, we review various optical biosensing strategies based on enzymes as recognition elements that were ingeniously designed and successfully utilized for OPs detection, with a particular emphasis on photoluminescence (PL), chemiluminescence (CL), electrochemiluminescence (ECL), and colorimetric (CM) biosensing strategies. We not only highlight the state-of-art developments and the construction strategies of the enzyme-based optical biosensing method but also summarize the existing deficiencies, current challenges, and the future perspectives of OPs detection.

1. Introduction

Organophosphorus pesticides (OPs), as one of the most critical and common agrochemicals, are widely used in agriculture due to their outstanding ability in controlling, prevent, or eradicate pests [1]. According to the market report conducted by Mordor Intelligence, the global demand for OPs was estimated at USD 7.06 billion in 2017, and the compound annual growth rate was expected to be 5.5% in 2018–2023 [2]. Despite their superb value, the overuse and abuse or illegal use of high toxicity and difficulty degradable OPs can bring about severe residue problems in foodstuff and the environment [3], which threaten the cycle of the ecosystem even at trace levels [4]. In particular, OPs residues can accumulate through the food chains, as displayed in Fig. 1 [5], which can further cause various illnesses, allergies, physiological and genetic disorders [6]. Consequently, it has become increasingly necessary to rapidly monitor the residual OPs in drinking water, food products, and human samples to control food safety, protect the ecosystem and prevent disease [7]. Till now, much work has been done to explore alternative methods in an attempt to satisfy this requirement. Biosensors have been successfully developed as analytical tools that can provide real-time quantitative and qualitative information about OPs with minimum sample preparation [8]. A biosensor comprises two main components, including a biological recognition element that specially interacts with the target analyte and a transducer that converts the recognition event into a measurable signal. Different types of bio-recognition elements such as antibody [9], aptamer [10], and enzyme [8] combined with electrochemical or optical sensing strategies have been used for the detection of OPs. The antibody has an extremely high affinity and specific binding to OPs. Nevertheless, the antibody suffers from some limitations due to the poor solubility, low thermal stability, thermal-induced aggregation, and retention of binding affinity at high temperatures [11]. Aptamer offers several advantages such as cost-effective, animal-free production, ease of chemical modification, good stability, strong affinity, and high selectivity [12]. However, aptamer-based biosensors could only recognize several kinds of OPs due to the difficulty in aptamer screening [13]. Compared with antibody and aptamer, the enzyme has higher specificity and sensitivity, simpler operation, faster response, and cheaper instrumentation. Nevertheless, enzyme possesses poor stability under harsh conditions [8]. Electrochemical sensing strategy possesses many advantages such as high reliability, basic instruments, rapid results, ease of operation, high sensitivity, and compatibility with complex samples [14], but low

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specificity, a requirement of high potential, and fouling problems still limited their wide utilization [15]. The construction of optical sensing strategy has provoked enormous attention due to the simple, rapid and, easy collection of signal change by fluorescence spectrophotometer or UV–vis spectrophotometer, even naked eyes [16]. Moreover, among the numerous optical biosensing methods that have been established, the enzyme-based optical biosensors are desirable for real-time and on-site detection as they are simple to manufacture and deploy as well as their high sensitivity and specificity catalysis ability [17].

Kaur et al. [8] reviewed enzyme-based optical biosensors for organophosphate class of pesticide detection, with emphasis on fluorescent biosensors using acetylcholinesterase (AChE) and organophosphorus hydrolase (OPH) as recognition elements. We focus on the construction of optical biosensors for OPs detection using various enzymes as biorecognition elements, with a particular emphasis on photoluminescence (PL), chemiluminescence (CL), electrochemilumin escence (ECL), and colorimetric (CM) biosensing strategy (Fig. 2). We not only highlight the latest advance of various enzymes that have been utilized as biorecognition elements in the fabrication of optical biosensing platforms and the efforts that have been made to improve the selectivity and sensitivity but also address existing deficiencies, current challenges, and future perspectives of OPs detection.

2. Various enzymes used as bio-recognition elements in optical biosensors for the determination of OPs

Various enzymes have been successfully employed as biological recognition elements in OPs optical biosensors because of their high specificity, high robustness, fast response, and easiness of immobilization [18]. In enzyme-based optical biosensors, OPs can be determined through i) an inhibition mechanism (Fig. 3A) ii) a catalytic hydrolysis mechanism (Fig. 3B). AChE [19], butyrylcholinesterase (BChE) [20], esterase-2 (EST2) [21], tyrosinase (TYR) [22], urease (URE) [23], acid phosphatase (ACP) [24], alkaline phosphatase (ALP) [25], and trypsin (TRY) [26] have been widely used in the method of their activity inhibition by OPs, while OPH [27] and phosphatase mimic [28] have been utilized in catalytic hydrolytic OPs. Except for the utilization of a single enzyme, bi-enzyme-based optical biosensors have been established, which depended on the cascade catalysis reaction of AChE and choline oxidase (CHO) [29].

2.1. Bio-recognition enzymes based on their activity inhibited by OPs

In the case of enzyme inhibition-mediated optical biosensors, the hydrolysis of substrates can cause a response to the optical signal. While in the presence of OPs, the enzymatic activity is inhibited so that the hydrolysis of substrates is inhibited, resulting in opposite optical signal response. It should be noted that this mechanism cannot be used for quantitation of an individual of OPs due to the universal mechanism and the similar structures of targets. Thus, they provide information about the OPs family rather than an individual component of the family [3].

2.1. 1. AChE, BChE, and EST2

AChE has been extensively used for OPs detection because of its specificity, simplicity, fast response, and easy on-site analysis [30]. In the AChE-based platforms, the reaction is as follows: acetylthiocholine + $H_2O \xrightarrow{AChE}$ thiocholine + acetate acid. AChE can catalyze the hydrolysis of acetylthiocholine (ATCh) into thiocholine (TCh), which specifically reacts with fluorophore [31], metal cations [32], nanomaterials [33], chromogenic reagent [34], and oxidant peroxydisulfate [35] resulting in the change of optical signal. In addition, it was shown that acetic acid produced in enzymatic reactions could cause pH decrease, which leads to fluorescence (FL) quenching for pH-sensitive QDs. BChE, as another form of cholinesterase can also be employed for OPs determination based on the same mechanism [36]. Nevertheless, compared with AChE, inhibitors are higher affinity and more selective for AChE because of the presence of more aromatic amino acids. Furthermore, EST2 extracted

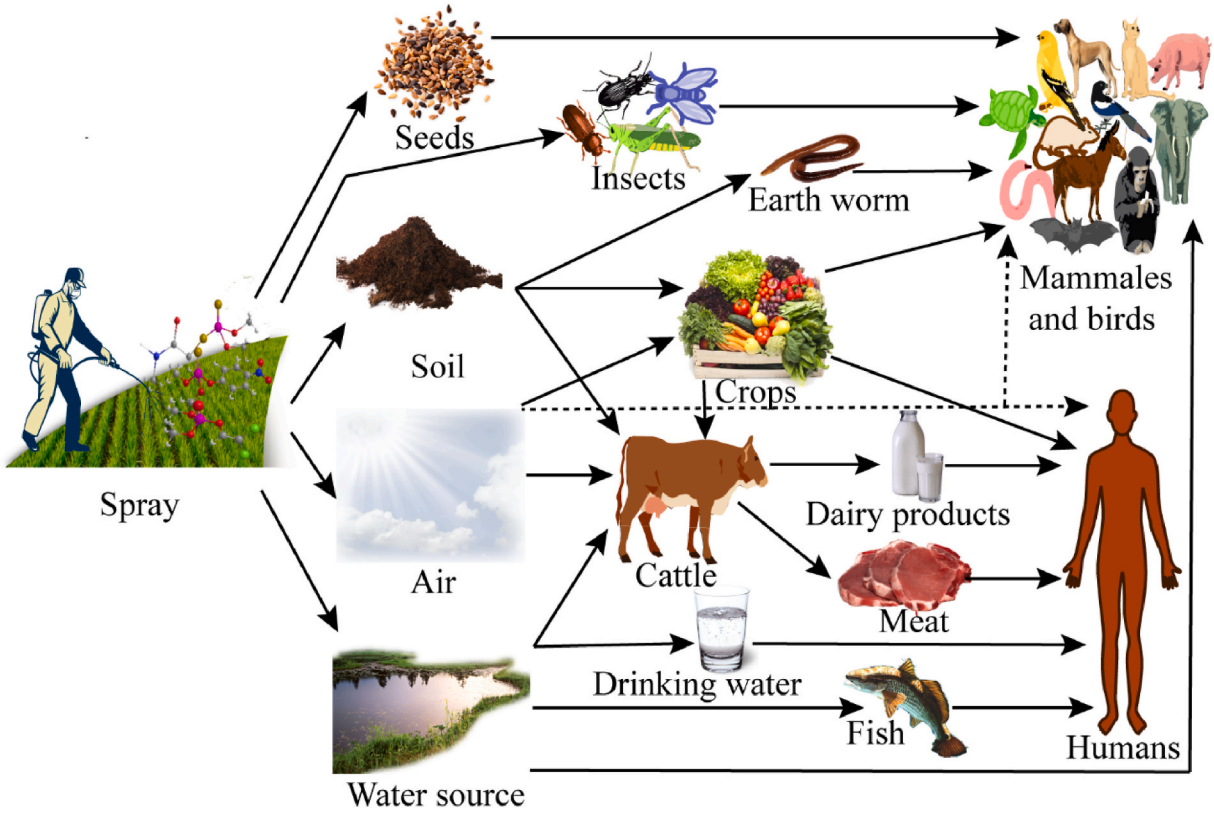

Fig. 1. Bio-concentration of residual OPs in the food chains (Reproduced with permission from Ref. [5]. Copyright 2018 Elsevier Ltd.).

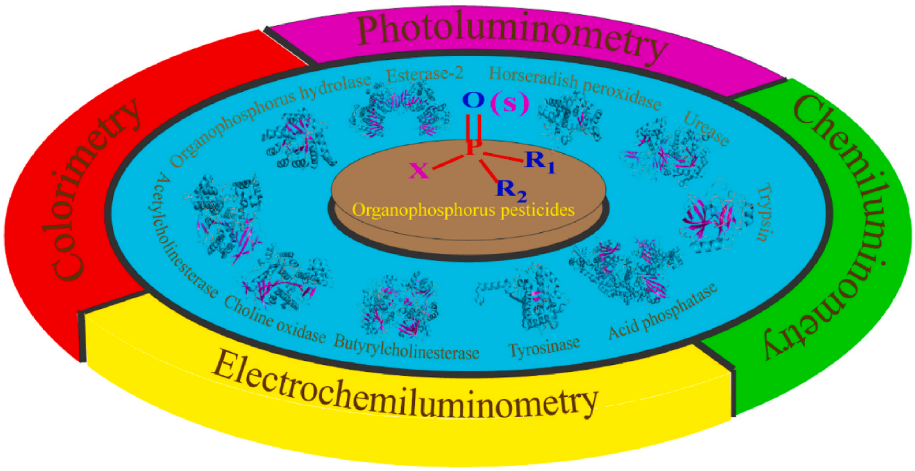

Fig. 2. Various optical biosensing strategies for the detection of OPs based on different enzymes.

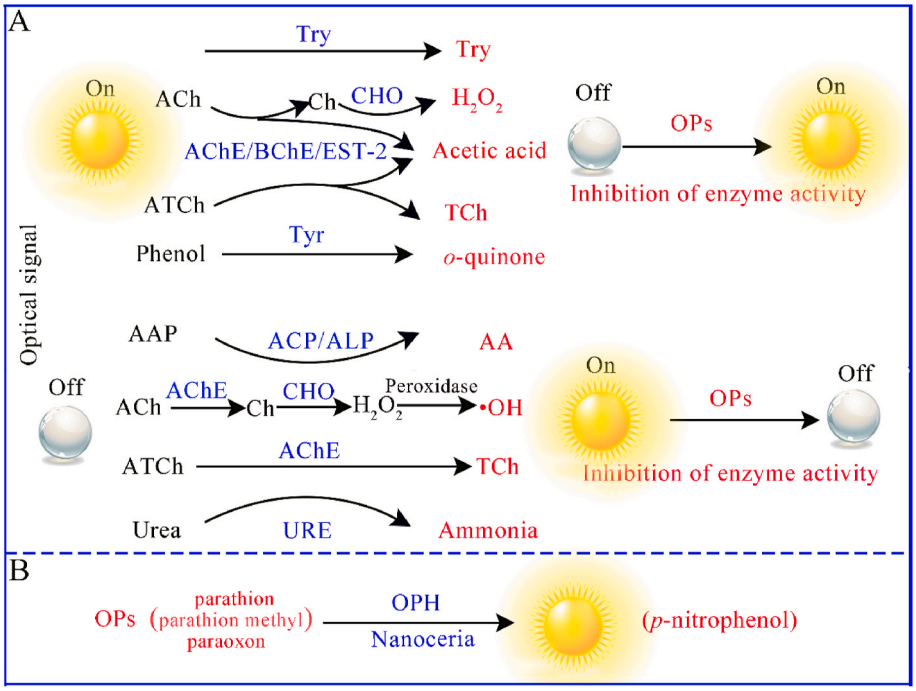

Fig. 3. Illustration of enzyme-based optical biosensors for OPs determination. A. Inhibition mechanism. B. Mechanism of catalytic hydrolysis.

from *Alicyclobacillus acidocaldarius* with AChE-like activity is also used for OPs detection, which not only possesses a better selectivity than AChE but also exhibits excellent resistance to temperature, detergents, and organic solvents [37].

2.1. 2. CHO

CHO is one kind of oxidase, which usually combines with AChE as the bi-enzyme cascade catalytic system for OPs detection [38]. The catalytic reactions are as follows: acetylcholine + $H_2O \xrightarrow{AChE}$ choline + acetate acid, choline + $O_2 + H_2O \xrightarrow{CHO}$ betaine + H_2O_2. H_2O_2 as the final product can directly quench the fluorophore, react with fluorescent dyes to emit FL, or change the color of the chromogenic substrates with the assistant of peroxidase. While in the presence of OPs, the activity of AChE and the generation of H_2O_2 are inhibited, resulting in a variable optical signal. Moreover, compared with sole enzyme biosensors, bi-enzyme cascade catalytic systems with the advantage of dual-signal amplification have been considered as a selective and sensitive strategy for the construction of biosensors [13].

2.1. 3. TYR

TYR plays a critical role in the formation of melanin, which is associated with the cutaneous pigmentation and the browning of agricultural products after harvesting and processing [39]. TYR can catalyze the formation of catechol derivatives from phenolic compounds and then oxidize them to *o*-quinone [13]. The catalytic reaction is as follows: phenolic + $O2 \xrightarrow{TYR} o -$ quinone. What's more, *o*-quinone can quench the FL of fluorophore. While in the presence of OPs, the generation of *o*-quinone is inhibited due to the inhibition of OPs on TYR activity [40], resulting in the recovery of the FL signal. Compared with AChE-based biosensors, TYR-mediated biosensing strategies have a better resistance for organic solvents and high temperatures [13].

2.1. 4. URE

URE derived from jack beans (*Canavalia ensiformis*) is one of the most

active ureases, which can efficiently catalyze the hydrolysis of urea into bicarbonate and ammonium [41]. As reported [23], ammonia could convert nonfluorescent copper nanoparticles (CuNPs) into green-emission fluorescent copper nanoclusters (CuNCs) through in situ etching process. As urease inhibitors, OPs prevented ammonia production and reduced in-situ corrosion of CuNPs, leading to a response of FL signal.

2.1. 5. ACP and ALP

ACP, as a digestive enzyme in mammalian body tissues and fluids, can efficiently catalyze the hydrolysis of phosphate monoesters in an acidic environment and release free phosphate groups [42]. The reaction is as follows: $\mathrm{L-ascorbic\ acid-2-phosphate\ (AAP)} \overset{\mathrm{ACP}}{\rightarrow}$ ascorbic acid (AA). As reported [43], the FL of quantum dots (QDs) could be quenched by quencher through Förster resonance energy transfer (FRET). However, ACP could catalyze the hydrolysis of AAP to AA, which could decompose the quencher, resulting in the recovery of the fluorescent signals. While in the presence of OPs, the activity of the ACP was blocked, restraining the generation of AA and the decomposition of the quencher. Thus, this biosensing strategy could be used for OPs determination. ALP can be utilized for OPs determination based on the same mechanism.

2.1. 6. TRY

TRY, extracted from the pancreas in high quantity, can cleave peptide chains mainly at the carboxyl side of the arginine or lysine [44]. Protamine is a small arginine-rich nuclear protein with a highly positively charged, which can be hydrolyzed by TRY [45]. Protamine could effectively bind to negatively charged AuNPs [46] or fluorescent probes [47] due to the electrostatic attraction, which leads to the aggregation of AuNPs or fluorescent probes resulting in a decrease of the optical signal. Upon the addition of TRY, protamine is degraded, resulting in AuNPs or fluorescent probe de-aggregates. In the presence of OPs, as a TRY inhibitor, a decreased optical signal recovery would be observed.

2.2. Bio-recognition enzymes based on catalytic hydrolysis of OPs

OPs, as catalysis substrate, can be metabolized by the enzyme and the concentration of OPs is determined through the response of the optical signal caused by hydrolysate.

2.2. 1. OPH

OPH is a promising candidate for the determination of OPs due to its ability to act on a wide range of substrates with various bonds, like P–S, P–O, P–F, and P–CN [48]. OPH possesses the capability to hydrolyze some OPs (such as PM, parathion, and paraoxon) together with producing low toxic products, such as diethyl phosphate and *p*-nitrophenol [121]. In most cases, the hydrolysates are rich in chromophores or cause changes in the signal intensity of other chromophores [50]. It is possible to detect OPs by directly monitoring the response of the optical signals due to the degree of change in signal intensity is proportional to the concentration of OPs. Differing from the other enzymes, OPH can catalyze the hydrolysis of OPs with high selectivity, turnover rate, fast response time, and can be reused [49].

2.2. 2. Nanoceria

Nanoceria, as a remarkably versatile rare earth material, has attracted widespread attention due to the two oxidation states between Ce^{3+} and Ce^{4+} [50]. The phosphatase mimic activity of nanoceria can catalyze the hydrolysis of OPs containing *p*-nitro functional groups to *p*-nitrophenol with chromogenic properties. Nanoceria possesses several advantages such as low cost, chemical stability, and easy to large-scale preparation compared with natural enzymes. Most importantly, Nanoceria exhibited better adaptability over a wide pH range and high-temperature resistance. In addition, Nanoceria delivered high catalytic stability against various interference ions. Despite the unsatisfied selectivity and efficiency, nanoceria materials still promise to replace natural phosphatases for a wide range of applications [51].

Although enzyme-based optical biosensing methods have been widely used in OPs detection, there are still some limitations such as (1) the activity of enzymes easily lose under harsh environmental conditions, (2) the activity may not be precise due to regeneration of enzymes, (3) lifetime of enzymes based biosensor is short [15], (4) no less than two reactions are involved (hydrolysis of the substrate, enzyme inhibition, or oxidation to produce hydrogen peroxide) [4], (5) purification of enzymes is quite costly and time-consuming.

3. Enzyme-based optical biosensing strategy for OPs detection

At present, there are various enzyme-based optical biosensors for OPs detection. The current well-established enzyme-based optical biosensing strategies for OPs determination can be divided into four categories based on the features of transducing mechanism and signal output formats as PL, CL, ECL, and CM biosensing strategy.

3.1. Photoluminescence biosensing strategy

PL is defined as the light emission due to the excitation of light. Generally, there are two categories: down-conversion (DC) luminescence (usually called fluorescence luminescence) and up-conversion (UC) luminescence. DC luminescence is a stokes process that the ground-state electron absorbs a short-wavelength photon, and a long-wavelength photon will be emitted. While UC luminescence is the reverse process to DC luminescence. Lanthanide-doped up-conversion nanoparticles enable anti-stokes emission via nonlinear processes, where low-energy excitation photons in the near-infrared window can be upconverted into high-energy emission ones in the visible or ultraviolet regions. The unique capacity of up-conversion nanocrystals to undertake near-infrared excitation, amalgamated with their excellent luminescent characteristics, such as massive anti-stokes spectral shift, sharp emission band, multicolor emission, and long luminescence lifetime, makes these nanomaterials prime candidates for a plethora of applications [52].

3.1. 1. Fluorescence biosensing strategy

FL biosensing strategy has been extensively employed in OPs detection. With the development of science and technology, many materials have been used as fluorophores, including fluorescent dyes [53], semiconductors nanomaterials [54], metal nanomaterials [55], carbon nanomaterials [56].

Quantum dots (QDs), defined by the diameter size of less than 10 nm, have been the core concept of nanoscience and nanotechnology since their inception. QDs exhibit exceptional optical properties which impart distinct advantages over traditional fluorescent organic dyes not only due to broadly tunable excitation and narrow emission spectra, signal brightness, and photo-stability. QDs can greatly enhance the analytical performances of biosensors. QDs are being developed not only because of their ability for signal enhancement but also because of their high capacity for functionalization with bio-receptors [57]. During the detection process, the quenching mechanisms of QDs include pH-induced quenching [58], static quenching (SQ) [59], aggregation-induced quenching (AIQ) [55], dynamic quenching (DQ) [60], FRET [33], electron transfer (ET) [61], photoluminescence resonance energy transfer (PRET) [62] and inner filter effect (IFE) [54]. Meanwhile, OPs detection is carried out by fluorescent signal “turn on”, “turn off”, and “ratiometric” mode, which stands for the FL signal enhancement, decline, and proportionality due to the introduction of OPs respectively. The main formats of OPs FL biosensing strategies based on the enzymatic reaction from 2015 to 2021 are presented in Table S1.

3.1.1.1. "Turn on" mode. In the case of "turn on" mode, the hydrolysates of enzyme-catalyzed can directly cause FL quenching. While in the presence of OPs, the activity of enzymes is inhibited, leading to FL recovery (Fig. 4A–F). Cai et al. [58] synthesized a pH-sensitive FL probe that was derivative of tetraphenylethene (TPE) with one aldehyde group exhibiting different aggregation-induced emission effects in different pH solutions. Acetic acid, as a hydrolysate of ATCh catalyzed by AChE, could reduce the pH of the solution resulting in the protonation of TPE-1 and the decrease of fluorescent intensity. OPs inhibited the activity of AChE and the generation of acetic acid, which restrained the protonation of TPE-1 and recovered the FL (Fig. 4A). This proposed TPE-1 was utilized to determine dimethoate in a linear range from 9 to 22,500 ng mL^{-1} with a limit of detection (LOD) of 8 ng mL^{-1}. This work provides a new strategy for constructing a pH-sensitive FL biosensing method. Liang and Han [55] developed a novel FL biosensing strategy for OPs detection by combining protein templated gold nanoclusters (AuNCs) and yeast surface-displayed AChE mutants (Fig. 4B). Yeast surface-displayed AChE could catalyze the hydrolysis of ATCh to TCh. The positively charged TCh could not only bind with AuNCs through the S–Au bond but also absorb AuNCs by the electrostatic interaction, resulting in the aggregation of AuNCs and corresponding FL quenching. Paraoxon inhibited the activity of AChE and reduced the TCh-induced aggregation of AuNCs. This platform was used to more sensitive detect paraoxon with a LOD of 3.3×10^{-5} nM [55]. This strategy combines the functional bio-nano materials with the enzyme-modified surface display system of microorganisms, which provides an interesting way for ultra-sensitive, simple, and economical detection. On the contrary, Kaur et al. [63] developed an aggregation induced emission (AIE) based biosensor using TRY as biorecognition elements. AIE property of Su-TPE/PrS system composed of tetra-anionic sulphonyl derivative of tetraphenylethylene (Su-TPE) and cationic polyelectrolyte protamine (PrS), assembling by electrostatic interactions without any complex process of integration. Su-TPE/PrS fluorescence was quenched due to TRY-dependent PrS hydrolysis. However, the activity of TRY was inhibited in the presence of OPs, leading to the recovery of fluorescence. The commendable performance of the Su-TPE/PrS biosensor will enhance future development of rapid detection of trypsin along with fast high throughput screening of OPs. In addition, the catalytic hydrolysate of TYR can also quench FL. Yan et al. [22] constructed an FL biosensing platform by TYR-controlled quenching of AuNCs (Fig. 4C). The chicken egg white was used as a stabilizer and template to synthesize AuNCs by a one-step green synthetic method. This FL biosensing platform was demonstrated to enable rapid determination for OPs. Significantly, the FL probe was utilized to fabricate paper-based test strips for the visual determination of OPs, which validated the promising candidate for on-site and real-time applications.

Moreover, the hydrolysates of enzyme-catalyzed can also react with other reagents to generate substances that can quench FL. While in the presence of OPs, the enzyme's activity is inhibited, leading to FL recovery. Based on this mechanism, Li et al. [60] designed a biosensing platform for the determination of OPs via fluorometric and colorimetric pathway based on AChE-controlled quenching of FL carbon dots (CDs)

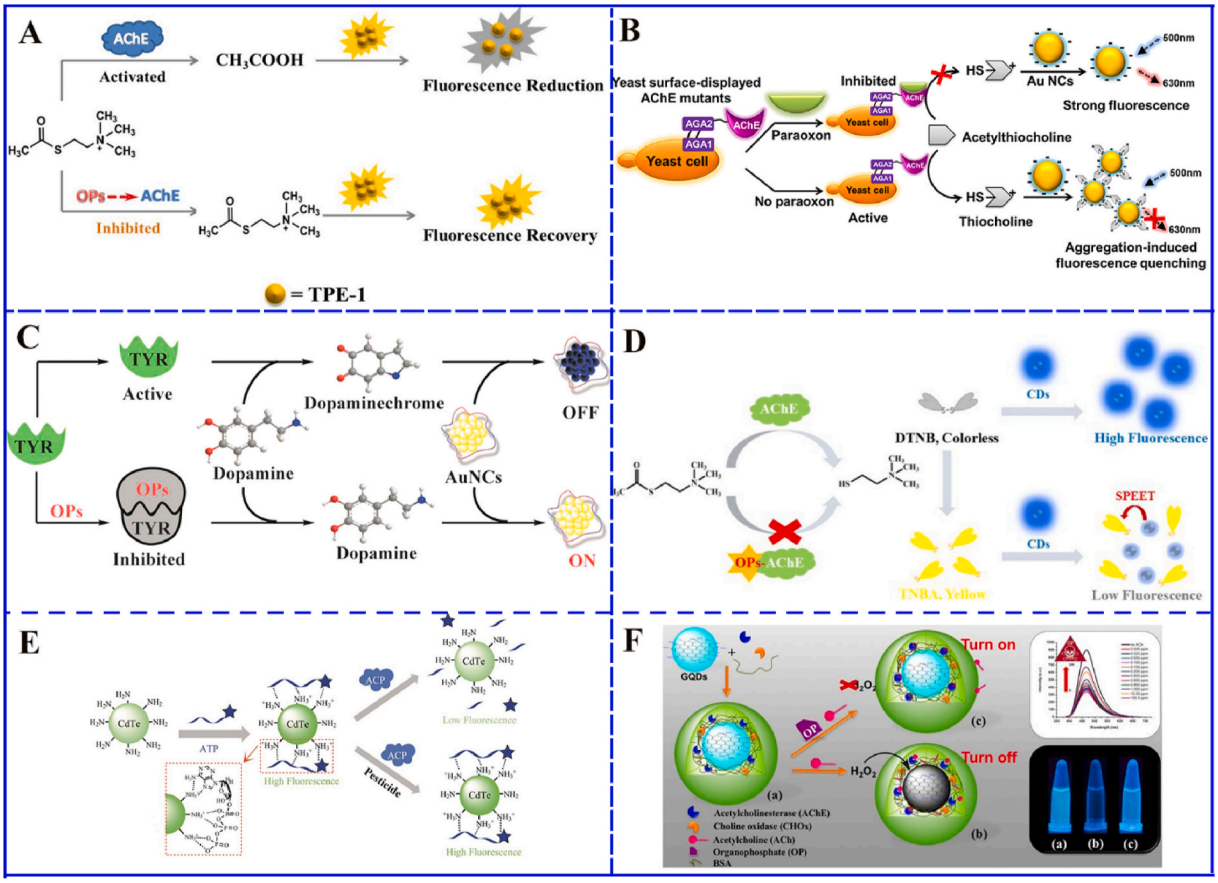

Fig. 4. Schematic illustration of FL biosensing strategies for the assays of OPs based on "turn on" mode. A. pH-induced fluorescence quenching method with inhibiting the formation of AChE hydrolysates (Reproduced with permission from Ref. [58]. Copyright 2019 Elsevier Ltd.); B. AIQ method with inhibiting the generation of AChE hydrolysates (Reproduced with permission from Ref. [55]. Copyright 2020 Elsevier Ltd.); C. DQ method with inhibiting the generation of TYR hydrolysates (Reproduced with permission from Ref. [22]. Copyright 2017 Elsevier Ltd.); D. DQ method with a dual-readout assay for OPs (Reproduced with permission from Ref. [60]. Copyright 2018 Elsevier Ltd.); E. SQ method with inhibiting the hydrolysis of ACP substrates (Reproduced with permission from Ref. [24]. Copyright 2016 Elsevier Ltd.); F. FRET strategy with inhibiting the generation of hydrolysates of bi-enzyme cascade catalysis system (Reproduced with permission from Ref. [64]. Copyright 2018 Elsevier Ltd.).

(Fig. 4D). TCh, as a product of AChE catalytic hydrolysis of ATCh, could decompose 5,5-dithiobis (2-nitrobenzoic acid) (DTNB) to yellow-colored 5-thio-2-nitrobenzoic acid (TNBA). Meanwhile, TNBA could quench the FL of CDs through the DQ process. OPs could inhibit the activity of AChE, resulting in a decrease in absorbance intensity and the recovery of the FL. The dual-output method exhibited sensitivity for the rapid determination of paraoxon with a LOD of 0.4 ng mL^{-1}. The dual-output biosensing platform overcomes the deficiency of low anti-interference capacity and relatively poor stability of metal NPs-modulated biosensors. Meanwhile, the dual signal response in one biosensing platform can provide an additional correction of output signals.

In addition, the substrates of enzymatic hydrolysis also play an important role in the "turn-on" mode. Wang et al. [24] constructed a biosensing platform based on the FL enhancement mode of cysteamine-capped CdTe QDs for PM detection (Fig. 4E). Upon addition of ATP, the amino groups on the surface of CdTe QDs could form hydrogen bonding and electrostatic with ATP, resulting in FL enhancement of QDs. The hydrolysis of ATP into phosphate fragments and adenosine could be catalyzed by ACP under an acidic solution, leading to a decrease in the FL intensity of QDs. PM could inhibit the activity of ACP, which restrained the hydrolyzation of ATP resulting in the FL recovery. The proposed platform showed good sensitivity for PM with a LOD of 0.5 ng mL^{-1}.

The bi-enzyme system with the advantage of dual-signal amplification has been considered as a selective and sensitive strategy for the fabrication of optical biosensing platforms. H_2O_2, generated from ACh under AChE/CHO cascade catalysis system, can quench the FL of QDs through PRET. OPs can suppress the activity of AChE, resulting in a decrease in the quenching rate. On this basis, Sahub et al. [64] developed a graphene quantum dots (GQDs) and bi-enzyme with bovine serum albumin (BSA) platform for monitoring the OPs (Fig. 4F). This biosensor highlighted the rapid determination of dichlorvos with a LOD of 0.172 mg L^{-1}. This proposed optical biosensor is low cost, utilizes non-toxic materials, is easy-to-prepare, and is convenient to use without unstable and expensive dye. Based on the bi-enzyme systems, various nanomaterials such as Mn-doped ZnSe QDs [65], SiQDs [66], CdTe QDs [67], and CDs [68] were used as FL reporters for OPs determination.

The proposed protocol with a "turn-on" mode is convenient, simple, low toxicity, and has good reliability, which could effectively reduce the false-positive signals [69].

3.1.1.2. "Turn off" mode. In "turn off" mode, the hydrolysates of enzyme-catalyzed can interact with some quenchers resulting in FL recovery, or directly causing the fluorophore to generate FL. When OPs exist, the catalysis of enzymes and the formation of enzyme-catalyzed hydrolysates are inhibited, resulting in FL quenching (Fig. 5A–D). Qu et al. [43] constructed a label-free FL biosensing strategy for ACP and its inhibitor PM determination based on glutathione-functionalized GQDs (GQDs @GSH) (Fig. 5A). MnO_2 nanosheets could quench the FL of GQDs @GSH through FRET. ACP could catalyze the hydrolysis of AAP to AA, which decomposed MnO_2 nanosheets to Mn^{2+} in an acidic environment,

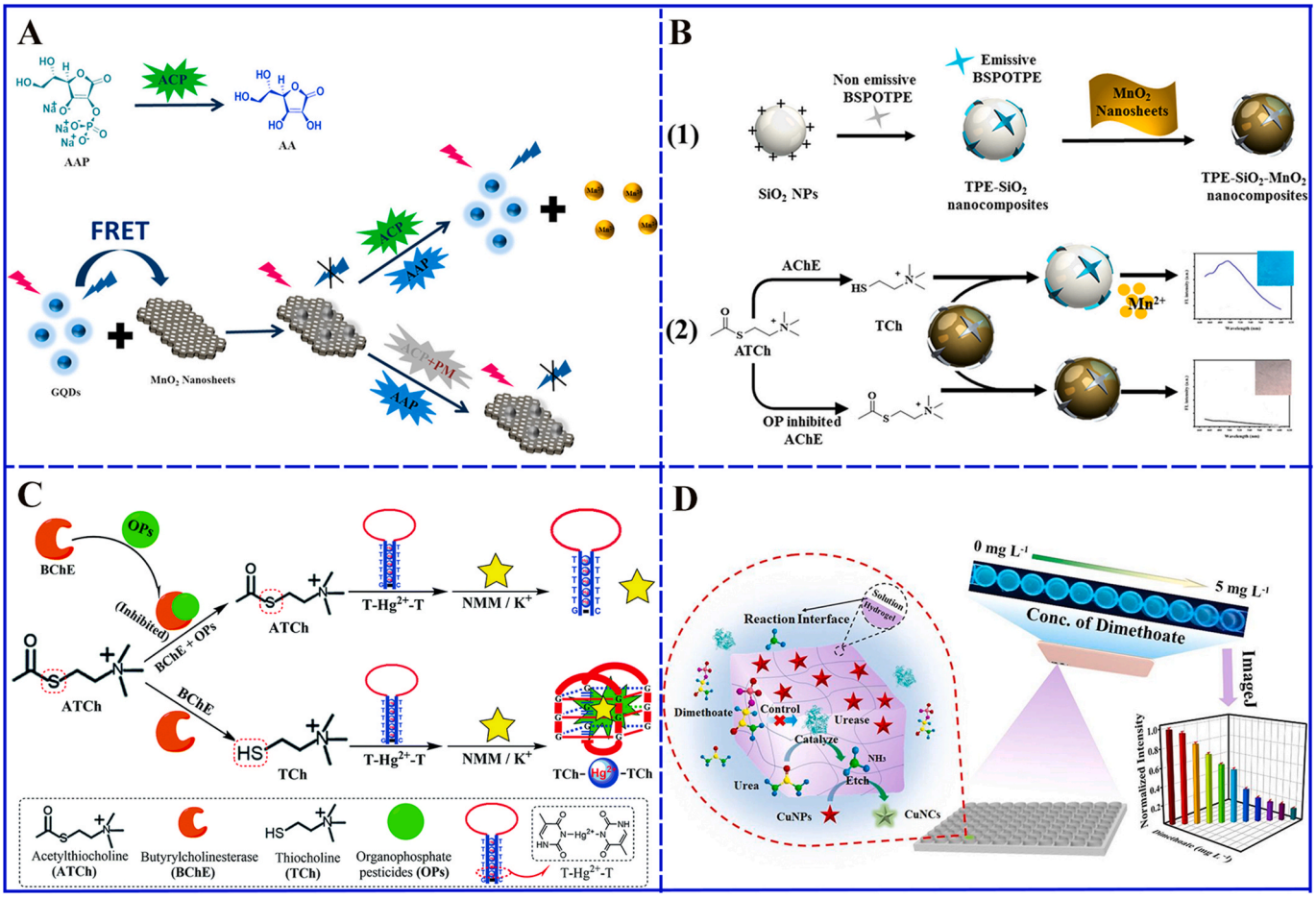

Fig. 5. Schematic illustration of FL biosensing strategies for the assays of OPs based on "turn off" mode. A. FRET strategy with inhibiting the generation of ACP hydrolysates (Reproduced with permission from Ref. [43]. Copyright 2019 Elsevier Ltd.); B. FRET method with inhibiting the generation of AChE hydrolysates (Reproduced with permission from Ref. [33]. Copyright 2019 Elsevier Ltd.); C. SQ strategy with inhibiting the hydrolysis of BChE substrates (Reproduced with permission from Ref. [59]. Copyright 2019 The Royal Society of Chemistry); D. In-situ etching method with restraining the generation of urease hydrolysate (Reproduced with permission from Ref. [23]. Copyright 2019 Elsevier Ltd.).

resulting in enhanced FL intensity. PM could inhibit the activity of ACP, which restrained the generation of AA and the decomposition of MnO_2 nanosheets, resulting in the FL quenching. Such a biosensing platform exhibited a linear range from 67 to 4570 ng mL^{-1} with a LOD of 16.9 ng mL^{-1}. The proposed method had potential application in the real sample detection of ACP and OPs with satisfactory results and good reproducibility. Similarly, MnO_2 nanosheets can also be decomposed by TCh produced by AChE or BChE catalytic hydrolysis ATCh [70]. Wu et al. [33] synthesized aggregation-induced emission fluorophores (AIEgens) using 1, 2-bis [4-(3-sulfonatopropoxyl) phenyl]-1, 2-diphenylethene (BSPOTPE) (Fig. 5B). AChE catalyzed the hydrolysis of ATCh to TCh, which could "turn on" the FL biosensor. Based on the inhibition

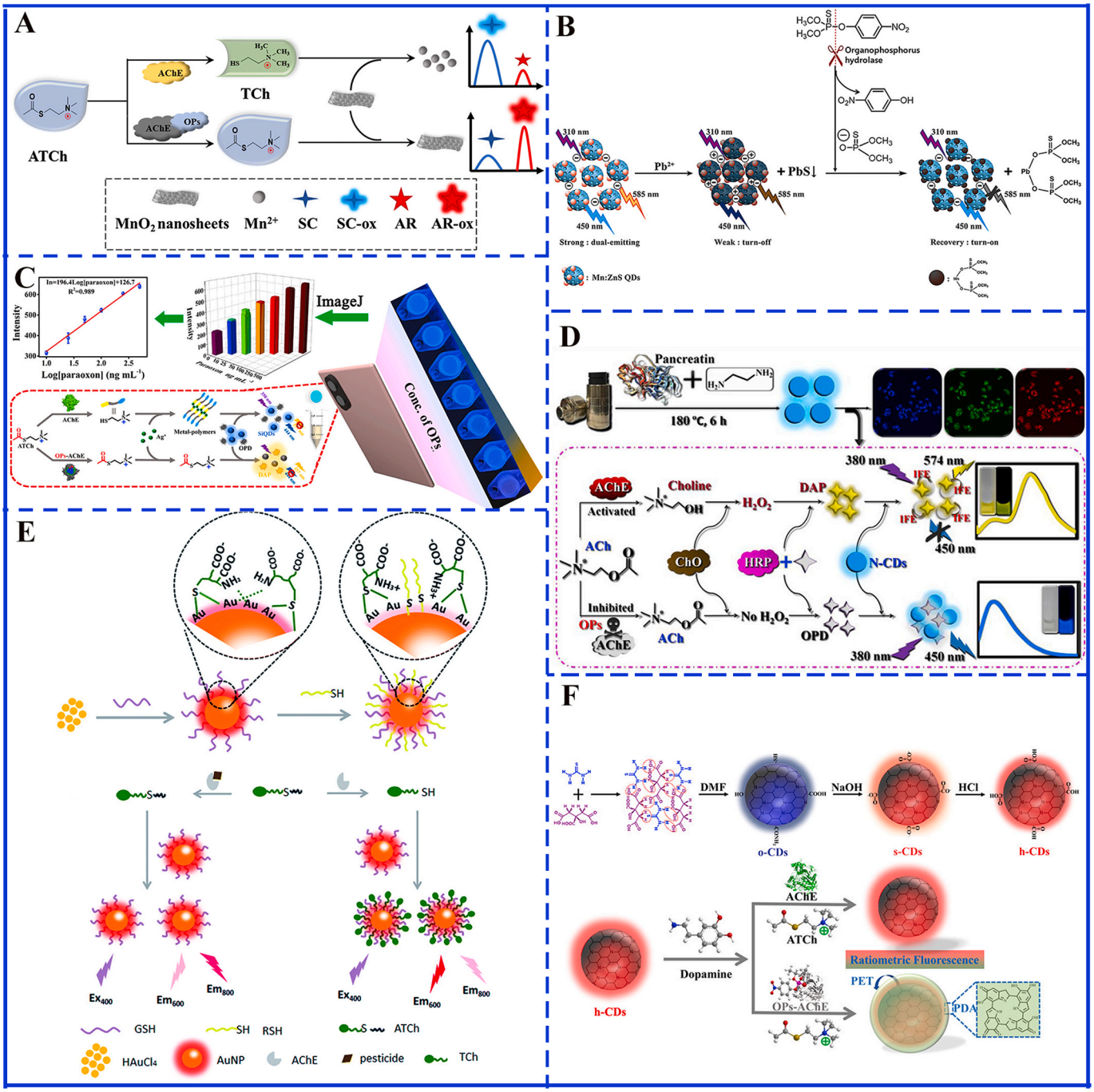

Fig. 6. Schematic illustration of FL biosensing strategies for the assays of OPs based on "ratiometric" mode. A. Construction of two organic fluorophores with an opposite signal response for the determination of OPs (Reproduced with permission from Ref. [73]. Copyright 2019 Elsevier Ltd.); B. Dual-emitting Mn-doped ZnS QDs strategy for the determination OPs through hydrolysis by OPH (Reproduced with permission from Ref. [75]. Copyright 2019 Elsevier Ltd.); C. Ratiometric signal of SiQDs and OPD hydrogels used as indicators for the determination OPs (Reproduced with permission from Ref. [54]. Copyright 2019 American Chemical Society.); D. IFE strategy between DAP and N-CDs for the determination of OPs (Reproduced with permission from Ref. [76]. Copyright 2019 American Chemical Society); E. Synthesis of the dual-emission AuNPs with opposite change for the determination of OPs (Reproduced with permission from Ref. [78]. Copyright 2019 The Royal Society of Chemistry); F. Red emissive CDs combined with AChE-mediated polymerization of DA for the determination of OPs (Reproduced with permission from Ref. [31]. Copyright 2020 American Chemical Society). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

effect of OPs on AChE activity and the corresponding "turn off" effect on the FL biosensor, an AIE-based assay for OPs detection was fabricated. The constructed biosensor for paraoxon detection exhibited a good linear range from 1 to 100 ng mL^{-1} with a LOD of 1 ng mL^{-1}. This "on-off" fluorescent biosensor is promising for on-site detection OPs through fabricating a simple, convenient fluorescence strip for visual semi-quantitative. Yuan et al. [59] developed a T-Hg^{2+}-T hairpin structure and enzymatic reaction-modulated formation of the G-quadruplex, which was further utilized for the FL biosensing for parathion detection (Fig. 5C). BChE could catalyze the reaction of ATCh to produce TCh, which could combine with Hg^{2+} in T-Hg^{2+}-T. The released single-stranded DNA associated with K^+ and N-methyl mesoporphyrin IX (NMM) to form a G-quadruplex, producing a strong FL signal. Parathion could inhibit the activity of BChE, which restrained the generation of TCh, resulting in less or no release of the free DNA probe. Therefore, most of the DNA probe maintained its T-Hg^{2+}-T hairpin structure, which resulted in a significant decrease in the FL signal. Under optimum conditions, the LOD of OPs was 0.025 ng mL^{-1}. The proposed method provides several advantages, including highly sensitive and selective, simple, and cost-effective for label-free detection. Kong et al. [23] developed a stimuli-responsive hydrogel (SRHg)-based portable kit embedding CuNPs in agarose hydrogel for dimethoate detection (Fig. 5D). Dimethoate restrained the activity of urease and the generation of ammonia, which decreased the in-situ etching of CuNPs, leading to the FL signal response of the test kit. Interestingly, the photo image of the portable test kit could be translated into digital information utilizing ImageJ software through smartphone-based nano-colorimetry, achieving a direct determination of dimethoate. The SRHg-based portable test kit combined with smartphone-based color recognition not only improved the stability, sensitivity, and accuracy but also simplified the operation process and shortened analysis time, showing that this platform could meet the routine determination and provided a new sight for on-site monitoring.

However, the "turn off" mode is susceptible to interference from other substances in the matrix that can cause false signals or bias the test results.

3.1.1.3. "Ratiometric" mode. Ratiometric FL biosensing strategy, which determines the OPs by measuring the change of the ratios of FL intensities at two wavelengths, has attracted intense attention in recent years [31]. Ratiometric FL methods provide a built-in correction that eliminates false signals and thus possesses improved accuracy and sensitivity [71]. Furthermore, the ratiometric compare the FL intensity of two peaks regardless of the concentration of the biosensing system, thus can overcome intrinsic background FL intensity and the signal fluctuation in reagents [72]. Ratiometric FL biosensing strategy can be constructed by combining a dynamic fluorophore and a reference fluorophore, or they may have two dynamic fluorophores that change their signals in opposite directions (Fig. 6A–F). Yao et al. [73] constructed a ratiometric FL biosensor utilizing Amplex Red (AR) and scopoletin (SC) as probe pairs that have opposite signal responses to MnO_2 nanosheets (MnO_2NS) (Fig. 6A). MnO_2NS possessed catalytic activity of peroxidase-like, which could enhance the FL of the non-fluorescent substance AR by oxidation and quenched the FL of SC. AChE catalyzed the hydrolysis of ATCh into TCh, which caused the decomposition of MnO_2 NS to Mn^{2+}, decreasing the signal of AR and increasing the signal of SC. In the presence of OPs, the activity of AChE and the decomposition of MnO_2 NS were inhibited, therefore increasing the FL intensity of AR and decreasing the FL intensity of SC. Under optimum conditions, this strategy had a wider linear range from 5.0 pg mL^{-1} to 500 ng mL^{-1} with a LOD of 1.6 pg mL^{-1} for dichlorvos. This strategy also could be used as a visual detection based on the color change of the solution under UV light [73]. Unfortunately, some blemishes of these small organic fluorophores limit their further utilization. For instance, excitation backscattering effects and small stokes shifts lead to errors and self-quenching in FL determination, respectively [74]. Semiconductor QDs with narrow and tunable FL emission bands make them promising candidates for ratiometric determination. Zhang et al. [75] designed a ratiometric FL biosensing strategy based on dual-emitting Mn-doped ZnS QDs (Mn: ZnS QDs) for the determination of Pb^{2+} and PM (Fig. 6B). Pb^{2+} could quench the dual emitting Mn: ZnS QDs proportionally due to the aggregation effect. OPH hydrolyzed the PM into dimethyl-thio-phosphoric-acid (DMPA). The stronger coordinative interaction between the Pb^{2+} and DMPA resulted in FL recovery of the Mn: ZnS QDs-Pb^{2+} system. The FL intensity exhibited a linear range from 0.19 to 0.95 μM, with a LOD of about 0.02 μM for PM. The proposed biosensor system can be successfully applied for the detection of Pb^{2+} and MP residues in apple, lake water, and drilling water. In addition, compared with other previous methods, this method is more rapid, sensitive, and convenient without complicated surface modification. However, the low biocompatibility, intrinsic cytotoxicity, and poor water solubility of QDs restrict their further application. Jin et al. [54] established a convenient and simple portable kit for the determination of OPs based on Ag^+-responsive hydrogels (Fig. 6C). The synthesized hydrogels used SiQDs and o-phenylenediamine (OPD) as indicators, which exhibited a ratiometric signal response. OPs inhibited the activity of AChE and the generation of TCh, which restrained the formation of metal-polymer with Ag^+, further triggering the oxidation of OPD to yield yellow 2,3-diaminophenazine (DAP). DAP could quench the FL of SiQDs through the IFE process, emerging a ratiometric signal response. However, most of these metal-based FL biosensors are usually associated with a long preparation time, poor water solubility and stability, and potential cytotoxicity, which restricts their further utilization in complex food systems and environmental samples [76]. Huang et al. [76] fabricated selective and sensitive ratiometric fluorescent probe pairs for the detection of OPs based on the IFE between DAP and N-CDs (Fig. 6D). 1, 2-ethanediamine and pancreatin were used as precursors to synthesize N-CDs through a one-pot hydrothermal method. N-CDs showed negligible cytotoxicity and excellent FL properties, demonstrating their further biological utilization. Under optimum conditions, this ratiometric FL method showed relatively low LODs of 13 ng mL^{-1} for PM and 3.2 ng mL^{-1} for dichlorvos. The practical application of this ratiometric fluorescent probe to detect OPs was further verified in tap water and food samples with satisfying results. Till now, most ratiometric biosensors using fluorescent organic dyes are low FL QYs, susceptible to photobleaching, exhibit generally narrow excitation wavelength range and broad emission bands, and especially the complexity of synthesis and purification of organic molecular [77]. AuNPs as a new class of luminescent nanomaterials has attracted great attention in bioimaging and biosensing. Their small size, low cytotoxicity, good biocompatibility, excitation by visible light, and emission with a large stokes shift compared with QDs, make them promising nanomaterials for ratiometric biosensing and bioimaging in living cells [137]. Pan et al. [78] synthesized dual-emission AuNPs with a low emission at 600 nm and a high emission at 800 nm by adjusting an appropriate ratio of glutathione: $HAuCl_4$ (Fig. 6E). The sulfhydryl-containing compounds could lead to opposite changes to weaken the 800 nm emission and strengthen the 600 nm emission. AChE catalyzed the hydrolysis of ATCh into TCh, which could interact with AuNPs, causing the opposite change of the dual emissions. OPs inhibited the activity of AChE and the generation of TCh. Such a ratiometric biosensing platform showed an obvious sensitivity to chlorpyrifos with a LOD of 0.07 nM. Due to high sensitivity, good selectivity, and convenient operation, this designed assay based on dual emissive GS-AuNPs for enzyme activity detection and inhibitor screening may extend the application in bioimaging and other research fields. Li et al. [31] synthesized efficient red emissive CDs at 610 nm (QYs ca. 24.0%) from thiourea and citric acid based on the solvothermal treatment utilizing dimethylformamide as solvent (Fig. 6F). Surface engineering and the incorporation of nitrogen controlled by conjugating sp^2-domain played a critical role in the obtained red emission of CDs. These CDs were considered promising candidates to construct a

ratiometric fluorescent platform for detecting trace levels of OPs due to their abundant surface functional groups and excellent optical properties. Combining the AChE-mediated polymerization of DA and the inhibition of OPs toward the enzyme, the degree of polymerization of DA was proportional to the concentration of OPs. By measuring the ratio of FL signal intensity, the proposed platform exhibited robust performance and was highly selective in the pg L^{-1} level for paraoxon, parathion, and malathion. Compared with fluorescent organic dyes ratiometric biosensors, ratiometric fluorescent-quantum dots (RF-QDs) show several advantages, such as narrower spectral line-width, better stability under photobleaching, and easier preparation. Furthermore, RF-QDs are simply synthesized by combining two differently colored QDs in one nanoparticle, one kind of QDs as a signal report unit and another as a reference. Thus, RF-QDs can be used as powerful tools in biosensing.

3.1. 2. Up-conversion luminescence biosensing strategy

FL biosensing platforms based on CDs, nano-cluster (NC), and semiconductor quantum dots (SQDs) require high excitation energies, which will result in the instability of FL and bring errors to the FL measurement utilized in the quantitative analysis [56]. Hence, it is significant to design fluorescent probes with low energy excitation, red region emission, and stable FL intensity for the determination of OPs. UC luminescence may be an effective solution. In recent years, rare-earth-doped up-conversion nanoparticles (UCNPs) which are capable of converting near-infrared excitation to UV or visible emission through sequentially absorbing two or more low-energy photons, have attracted increasing attention due to their [79]. Firstly, UCNPs have long luminescence lifetimes, good biocompatibility and optical stability, low toxicity, and deep tissue penetration depth [80]. Secondly, UCNPs possess excellent physicochemical features, including high chemical stability, negligible photobleaching, large anti-stokes shifts, and under near-infrared excitation. In addition, UCNPs are free of auto FL interference from various sample matrixes, which provides a high signal-to-noise ratio and low background signal [81]. Liu et al. [82] constructed a TYR-mediated PET system for OPs determination by utilizing dopamine-functionalized UCNPs as fluorescent probes (Fig. 7A). The FL of UCNPs could be quenched by dopamine quinone produced by TYR-mediated oxidation of dopamine. OPs could inhibit the FL quenching due to the inhibition of TYR activity. Under optimum conditions, chlorpyrifos could be analyzed in a liner range from 1.0 to 1000 ng mL^{-1}, with a LOD of 0.38 ng mL^{-1}. Wang et al. [83] constructed an up-conversion FL biosensing platform for the determination of OPs based on the AChE modulated FL "off-on-off" strategy (Fig. 7B). Cu^{2+} could quench the luminescence of $NaGdF_4$: Yb/Tm through FRET. Upon the addition of AChE and ATCh, the hydrolysate could seize Cu^{2+} from the UCNPs-Cu^{2+} mixture, leading to the quenched FL being turned on. OPs inhibited the activity of AChE, which decreased the formation of TCh, thus, reduced the recovery of FL. Under optimal conditions, a linear range from 0.1 to 50 ng mL^{-1} was achieved for diazinon with a LOD of 0.05 ng mL^{-1}. Lin et al. [84] constructed a double-enzymes-modulated fluorescent assay based on the quenching of $NaYF_4$: Yb, Er UCNPs by Fe^{3+} for determination of OPs (Fig. 7C). OPs can inhibit the activity of AChE to reduce the production of choline and further lead to the lack of H_2O_2 in the presence of CHO. Therefore, Fe^{2+} cannot be converted into Fe^{3+}, resulting in the "turn-on" fluorescence of UCNPs. Under optimal conditions, a linear detection range from 20 to 2000 ng mL^{-1} was achieved for chlorpyrifos with a LOD of 6.7 ng mL^{-1}. Overall, the integration of UCNPs into the double-enzymes-mediated Fe^{3+}/Fe^{2+} conversion endows this method with desirable rapidity, selectivity, sensitivity, stability, operational simplicity, and strong anti-interference capability.

Unfortunately, PL still suffers low quantum yields and a short lifetime [85]. Additionally, an external light source is required, which may cause interference and related problems.

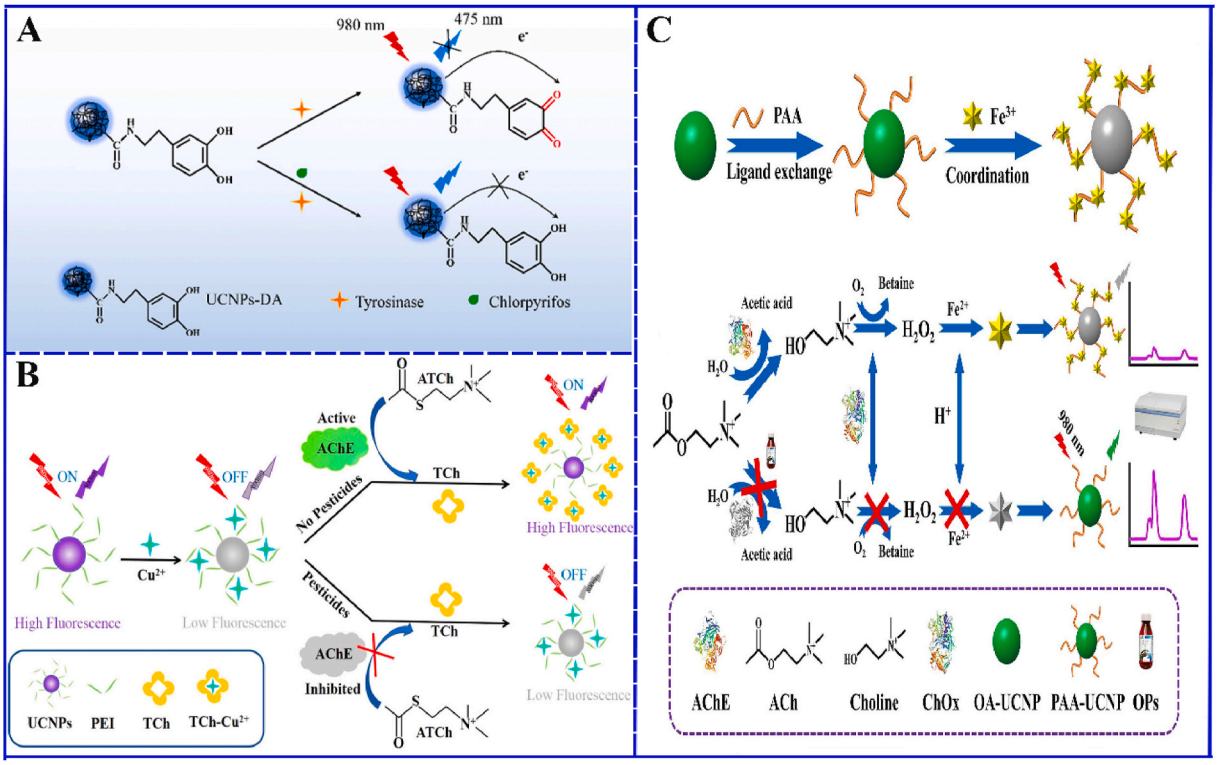

Fig. 7. Schematic illustration of UC biosensing strategies for the assays of OPs. A. TYR-mediated photo-induced electron transfer system with utilizing dopamine-functionalized UCNPs as fluorescent probes (Reproduced with permission from Ref. [82]. Copyright 2019 Elsevier Ltd.); B. $NaGdF_4$: Yb/Tm UCNPs capped with polyethyleneimine biosensing platform with AChE modulated FL "off-on-off" strategy (Reproduced with permission from Ref. [83]. Copyright 2019 American Chemical Society); C. A dual-enzymes mediated fluorescent approach combing NaYF4: Yb, Er UCNPs modified with carboxyl groups (Reproduced with permission from Ref. [84] Copyright 2021 Elsevier Ltd.).

3.2. Chemiluminescence biosensing strategy

CL is defined as the light emission from redox reactions in aqueous systems [86]. CL not only possesses high sensitivity and excellent LOD but also grants some advantages such as a lower background signal, problems related to external interferences due to not required external light source [87]. Insight of its ultimate significance and diversity of concrete applications, CL has been a striking strategy of intensive research in OPs detection. The main formats of OPs CL biosensing strategies based on the enzymatic reaction from 2015 to 2021 are presented in Table S2. The mechanism of CL is that AChE and CHO are used to catalyze ACh producing H_2O_2 and then react with the fluorescent probe to emit FL with the assistance of peroxidase [88]. Upon the inhibition of OPs on the activity of AChE, the generated H_2O_2 is decreased, which results in a decrease of the FL (Fig. 8A–C). Bagheri et al. [89] utilized Fe_3O_4 nanoparticles@ Zn-methyl imidazole metal-organic frameworks composite (Fe_3O_4 NPs@ZIF-8) with peroxidase-like was synthesized for the detection of OPs (Fig. 8A). The encapsulated Fe_3O_4NPs not only granted high peroxidase-like catalytic activity but also embraced high thermal and chemical stability. This fluorometric detection system with terephthalic acid (TA) as an FL probe showed a linear range from 0.5 to 500 nM with LOD 0.2 nM for diazinon. Furthermore, Fe_3O_4 NPs@ZIF-8 could be magnetically recovered and reused for at least ten cycles without an obvious decline in catalytic performance. In addition, they employed layered double hydroxides supported ZIF-8 nanocomposite (LDH@ZIF-8) with peroxidase-like activity for OPs detection (Fig. 8B). LDH@ZIF-8 exhibited an outstanding promoting effect on the CL emission intensity of the H_2O_2-rhodamine B system. The simple synthesized and low-priced LDH@ZIF-8 catalyst, as well as an easy-to-use and simple CL system, facilitated the development of a portable and on-site determination tool. A linear range from 0.5 nM to 300 nM with LOD 0.22 nM was achieved for the detection of diazinon [53]. Traditional CL is a flash type, disappearing quickly, and requiring strict conditions [90]. The glow type of CL has a long duration, which simplifies the measurements and operation. Lu et al. [91] constructed a long-lasting CL biosensing strategy for the determination of OPs. The strategy was based on N-(4-aminobutyl)-N-ethylisoluminol/Co^{2+} /chitosan (ABEI/Co^{2+}/CS) hydrogels, where MOF-Pt materials were selected as catalysts to improve the sensitivity (Fig. 8C). Firstly, the molecules diffused slowly, and the CL of the ABEI-H_2O_2 system was long-lasting because of the high viscosity of the hydrogels. Secondly, the CL intensity was increased by 6 times, 60% of which remained after 2 h under the synergistic effect of MOF-Pt. The linear range of this strategy was from 0.5 ng mL^{-1} to 1000 ng mL^{-1}, with a LOD of 0.21 ng mL^{-1} for chlorpyrifos. These results show that this sensing platform can be widely used for high throughput measurement of various OPs.

However, the development of some CL biosensing methods is limited due to the luminescence intensity is not strong enough to meet the determination requirements [92]. Furthermore, visible emission requires 40–70 kcal/mol, while only certain redox reactions can generate this much energy [93]. In addition, emission from CL reactions of inorganic molecules is relatively weak due to low QYs. Therefore, it is still needed to improve CL intensity for analytical applications [94].

3.3. Electrochemiluminescence biosensing strategy

ECL is a light emission process in which substances generated on the surface of the electrode undergo an exergonic electron-transfer reaction to form excited states and emit light [95]. In other words, ECL refers to CL triggered by an electrochemical method [96]. As it combines the advantages of electrochemical and chemiluminescent technology, ECL also avoids the problem of scattered light and exhibits nearly zero background noise [97]. In addition, ECL has many advantages, such as high sensitivity, simplified operation, and excellent temporal and spatial

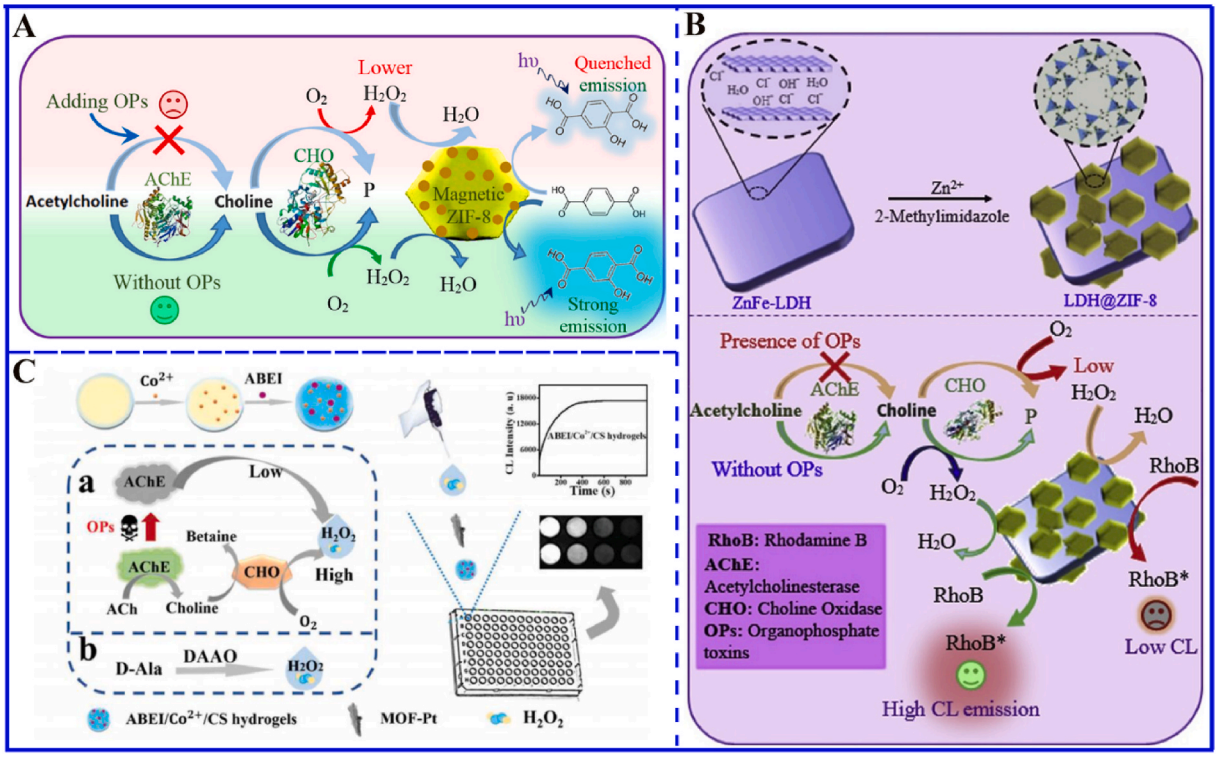

Fig. 8. Schematic illustration of CL biosensing strategies for the assays of OPs. A. Peroxidase-like of magnetic Fe_3O_4NPs encapsulated into ZIF-8 biosensing platform for the determination of OPs based on bi-enzyme modulated FL terephthalic acid - H_2O_2 system (Reproduced with permission from Ref. [89]. Copyright 2019 Elsevier Ltd.); B. Layered double hydroxides supported ZIF-8 with peroxidase-like activity for OPs detection (Reproduced with permission from Ref. [53]. Copyright 2019 Elsevier Ltd.); C. Illustration of long-lasting CL biosensing strategy based on N-(4-aminobutyl)-N-ethylisoluminol/Co^{2+}/chitosan hydrogels for the determination of OPs (Reproduced with permission from Ref. [91]. Copyright 2020 The Royal Society of Chemistry).

control on light emission [98]. The main formats of ECL biosensing strategies for OPs based on the enzymatic reaction from 2015 to 2021 are presented in Table S2. ECL consists of annihilation mechanism and co-reactant mechanism according to the source of radicals (Fig. 9A–D). In the annihilation pathway, radical species are generated from a single emitter on the surface of the electrode during a potential sweep. In the co-reactant pathway, radical species are generated from a bimolecular set of electrochemical reactions between a suitable co-reactant and the emitter [99]. The emitter plays an important role in the transformation of electrical energy into radiative energy.

3.3.1. *Annihilation pathway*

In the annihilation pathway, He et al. [29] constructed a co-reactant-free ECL biosensing platform for the detection of OPs utilizing poly (PFBT) functionalized with carboxyl groups (PFBT PNPs) as a luminophore (Fig. 9A). H_2O_2 generated from the enzymatic reaction could quench the ECL signal of PFBT PNPs, leading to an ECL signal-off state. OPs inhibited the activity of AChE, resulting in an ECL signal-on state. Such a platform exhibited a linear range from 1.0×10^{-3} to 1.0×10^{2} nM, with a LOD of 1.5×10^{-4} nM for OPs. This co-reactant-free ECL strategy not only avoided the drawbacks resulting from the dissolved O_2 or co-reactant but also had high sensitivity and a simple operation due to in situ generating a quencher. Moreover, there is no need to add exogenous species, which may cause stability or repeatability problems in the annihilation process. However, the annihilation pathway requires certain conditions to ensure efficient ECL. For example, a wide potential window is necessary for generating both radical anions and cations. In addition, the radical anions and cations must be stable enough for a long time to achieve electron transfer [96].

3.3. 2. *Co-reactant pathway*

In the co-reactant pathway, O_2, H_2O_2, peroxydisulfate ($S_2O_8^{2-}$) are the typical co-reactants in OPs detection. Enzyme-based ECL biosensing strategies mainly have three types: "signal-on", "signal-off", and "ratiometric" mode according to the different signal changes.

In the "signal-on" mode, the hydrolysate of enzyme-catalyzed or enzyme-catalyzed hydrolysis process is applied to consume the co-reactant. While in the presence of OPs, the enzyme activity is impeded, consequently suppressing the generation of hydrolysate and the consumption of co-reactant, which results in an enhanced ECL signal of luminophores. Wang et al. [35] constructed a sensitive ECL biosensing platform for OPs determination based on a nanocomposite carboxylated graphitic carbon nitride-poly (ethylenimine) (C-*g*–C_3N_4–PEI) and AChE (Fig. 9B). The obtained C-g–C_3N_4–PEI, which was synthesized through covalent bonding between the –NH_2 of PEI and the –COOH of C-g-C_3N_4, not only exhibited significantly enhanced ECL

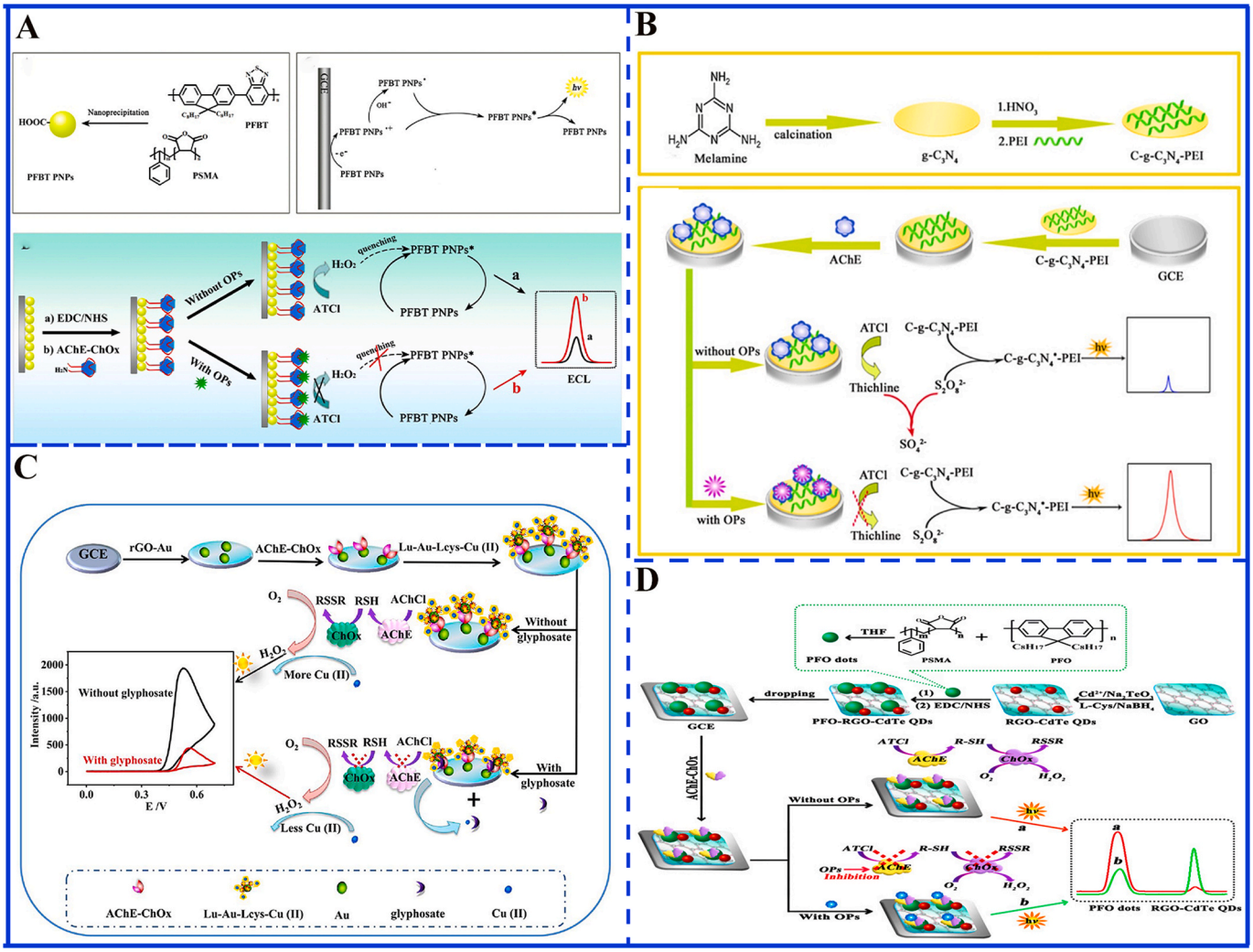

Fig. 9. Schematic illustration of ECL biosensing strategies for the assays of OPs. A. Co-reactant-free ECL biosensing platform utilizing PFBT PNPs as a luminophore (Reproduced with permission from Ref. [29]. Copyright 2019 Elsevier Ltd.); B. "Signal-on" mode utilizing $S_2O_8^{2-}$ as co-reactant (Reproduced with permission from Ref. [35]. Copyright 2017 Elsevier Ltd.); C. "Signal-off" mode utilizing O_2 as co-reactant (Reproduced with permission from Ref. [38]. Copyright 2020 Elsevier Ltd.); D. "Ratiometric" mode utilizing H_2O_2, and O_2 as co-reactant (Reproduced with permission from Ref. [101]. Copyright 2017 American Chemical Society).

stability and efficiency but also efficiently immobilized AChE through amide reaction. AChE could catalytically hydrolyze ATCl to TCh, which consumed co-reactant $K_2S_2O_8$, resulting in a decreased ECL signal. Since OPs inhibited the activity of AChE, resulting in the generation of TCh and the consumption of co-reactant $K_2S_2O_8$ were restricted, thus enhancing the ECL signal. Under optimal conditions, the proposed ECL biosensing platform exhibited a linear ranging from 1.0 pM to 5.0 mM with a LOD of 0.3 pM for ethyl paraoxon detection. The novel strategy has the advantages of fine practicality, good stability, and reproducibility, which might provide a new promise for OPs detection in real samples.

In "signal-off" mode, the co-reactant can be in situ generated through hydrolysis reaction or the hydrolysates of enzymatic-catalyzed can expedite in situ generations of luminophores. While in the presence of OPs, the enzyme activity is blocked, therefore, the generation of co-reactant or luminophores is inhibited, which results in a decreased ECL signal. Liu et al. [38] constructed a ECL biosensing platform based on double suppression for the determination of glyphosate (Fig. 9C). The graphene-gold nanoparticle composite (rGO-Au) was used as the capture substrate for AChE and CHO, and the luminol-gold nanoparticles-L-cysteine-Cu (II) composites (Lu-Au-Lcys-Cu (II)) were used as luminescent reagents to improve the luminescence ability of luminol. Meanwhile, Cu (II) in the composites could act as a peroxidase mimicking enhancing the ECL signal. When glyphosate was dropped on the above electrode, Glyphosate could inhibit the enzymatic reaction and impede the activity of the peroxidase-mimicking by competing with L-cysteine to form glyphosate-Cu (II) compound. Under optimal conditions, the linear range of glyphosate concentration was 1–1000 nM with LOD 0.5 nM. Importantly, the ECL biosensor also showed acceptable stability and selectivity.

Although these two methods have their advantages, inevitably, the signal changes may be affected by environmental conditions, resulting in false positive or negative errors [100]. The development of ratiometric ECL biosensors containing two ECL probes with different excitation potentials or excitation wavelengths can overcome this shortcoming. Chen et al. [101] developed a double-potential ECL ratiometry for OPs detection, which reduced graphene oxide-CdTe QDs (rGO-CdTe QDs) and carboxyl-conjugated polymer dots were chosen as cathodic and anodic ECL emitters respectively. The product (H_2O_2) of the enzymatic reactions and the dissolved O_2 served as their co-reactants, respectively (Fig. 9D). The rGO-CdTe QDs and polymer dots were utilized as a matrix for immobilizing AChE and CHO. Under the enzymatic reactions induced by the AChE and CHO, the anodic signal from PFO dots was at the "signal on" state because of the in-situ generation of H_2O_2. Meanwhile, the cathodic signal from rGO-CdTe QDs was at the "signal off" state because of the consumption of dissolved O_2. OPs could inhibit the activity of AChE and subsequently prevented the consumption of dissolved O_2 and the generation of H_2O_2, resulting in a decrease in anodic ECL signal and an increase in cathodic ECL signal. Under optimum conditions, ethyl paraoxon could be quantitatively detected with improved sensitivity, accuracy, and reliability in a linear range from 5×10^{-4} to 50 nM with a LOD of 0.125 pM.

Although many chemicals can act as co-reactants, only a few co-reactants are widely used in ECL biosensing systems because one must take into consideration the solubility, efficacy, and stability [96]. Hence, more research is required to design and identify new co-reactants. It is also necessary to continue to look for luminophores that not only possess equal stability but also have higher ECL efficiency at different wavelengths [99].

3.4. Colorimetric biosensing strategy

CM biosensing strategy has attracted wide attention due to its fast visual detection and easy readout by naked eyes, which can be applied to determine the targets based on the color change even at low concentrations for on-site screening without any aid of complex instruments [102]. The main formats of OPs CM biosensing strategies based on the enzymatic reaction from 2015 to 2021 are presented in Table S3. From the perspective of chromogenic substrates, enzyme-based CM biosensing strategies can be typically summarized as two types: One type is chromogenic reagents such as 3, 3′, 5, 5′-tetramethylbenzidine (TMB), OPD, Ce_2O_3, DTNB, indoxyl acetate (IDA) as probes. The other one is gold nanomaterials as chromogenic probes.

3.4. 1. Colorimetric biosensing strategy based on chromogenic reagents as chromogenic probes

CM biosensors mainly focus on chromogenic reagents such as DTNB, IDA, TMB, OPD, Ce_2O_3, which can be catalyzed into their corresponding colored products, yellow TNB, blue (2, 2′-biindoline)-3, 3′-dione (indigo dye), blue TMBox, orange OPDox, and yellow CeO_2, respectively [103] (Fig. 10A–D).

Ellman regents DTNB can react with TCH, the product of ATCh catalyzed by AChE, to produce yellow TNB. OPs can inhibit the activity of AChE, which restrain the generation of TCH and TNB, resulting in color reduction. Based on this principle, Cacciotti et al. [104] reported a multi-plated CM biosensing method for OPs determination based on the utilization of AChE as biological recognition component and biopolymeric electrospun fibrous mats as supports for AChE immobilization (Fig. 10A). This proposed biosensor consists of a novel, cost-effective, and multiplex-based 96-well plate, combined with customized biopolymeric membranes modified with AChE, aiming to deliver a sustainable analytical tool. Indeed, the designed system exhibited several advantages, including the re-use of plastic multi-plate with the only replacement of polymer dishes if the inhibition is absent and exploiting the characteristic of the immobilized enzyme, that is, using the same amount of enzyme for multiple analyses to reduce the amount of AChE. Under optimum conditions, this strategy achieved a linear range up to 60 ng mL^{-1} with a LOD of 10 ng mL^{-1} for paraoxon. The developed bioassay can deliver sensitive, rapid, and reproducible responses characterized by easiness to use, miniaturization, cost-effectiveness, and absence of sample clean-up, reducing both consumables and work time and satisfying environmental, health, and economical concerns.

The mechanism of IDA color change is that a single indoxyl radical produced by AChE is oxidized and makes a coupling with another indoxyl radical to yellow-colored 2,2'-biindoxyl, which reversibly converts to blue indigo dye. Kim et al. [105] fabricated a three-dimensional paper-based biosensor for chlorpyrifos by layering three sheets of patterned plates. The paper-based assay is a promising candidate for real-time detection due to its low cost, lightweight, and disposable. OPs could inhibit the generation of blue color produced by the interaction between AChE and IDA. Under optimal conditions, the chlorpyrifos was sensitively detected within 5min. Moreover, the lifetime of the device was enhanced to 14 days after the fabrication. In addition, a three-dimensional paper circumvented drawbacks of the conventional paper devices such as multi-step operation, time-consuming, and the small area of the test zone.

TMB, OPD, and Ce_2O_3 can be oxidized by H_2O_2 into blue TMBox, orange OPDox, and yellow CeO_2 respectively, in the presence of peroxidase. However, natural enzymes have inherent limitations, such as poor sensitivity and instability in harsh conditions, which restrict the application in biosensing. Fortunately, as an alternative to the natural enzyme, nanozymes with robust intrinsic peroxidase-like catalytic activity and high stability have been widely applied in CM biosensors to enhance the selectivity, sensitivity, and stability [106]. In the nanozyme-based CM biosensing system, TCh, as the catalyzed hydrolysate of ATCh by AChE, can inactivate peroxidase-like nanozymes. While in the presence of OPs, the activity of AChE and the generation of TCh are inhibited, leading to an increase in the absorbance of chromogenic reagents in the presence of H_2O_2. Furthermore, H_2O_2 can be generated in situ by the bi-enzyme system of AChE and CHO catalyzed ACh. In the presence of OPs, the activity of AChE and the generation of H_2O_2 are inhibited, causing a decrease in the absorbance of chromogenic

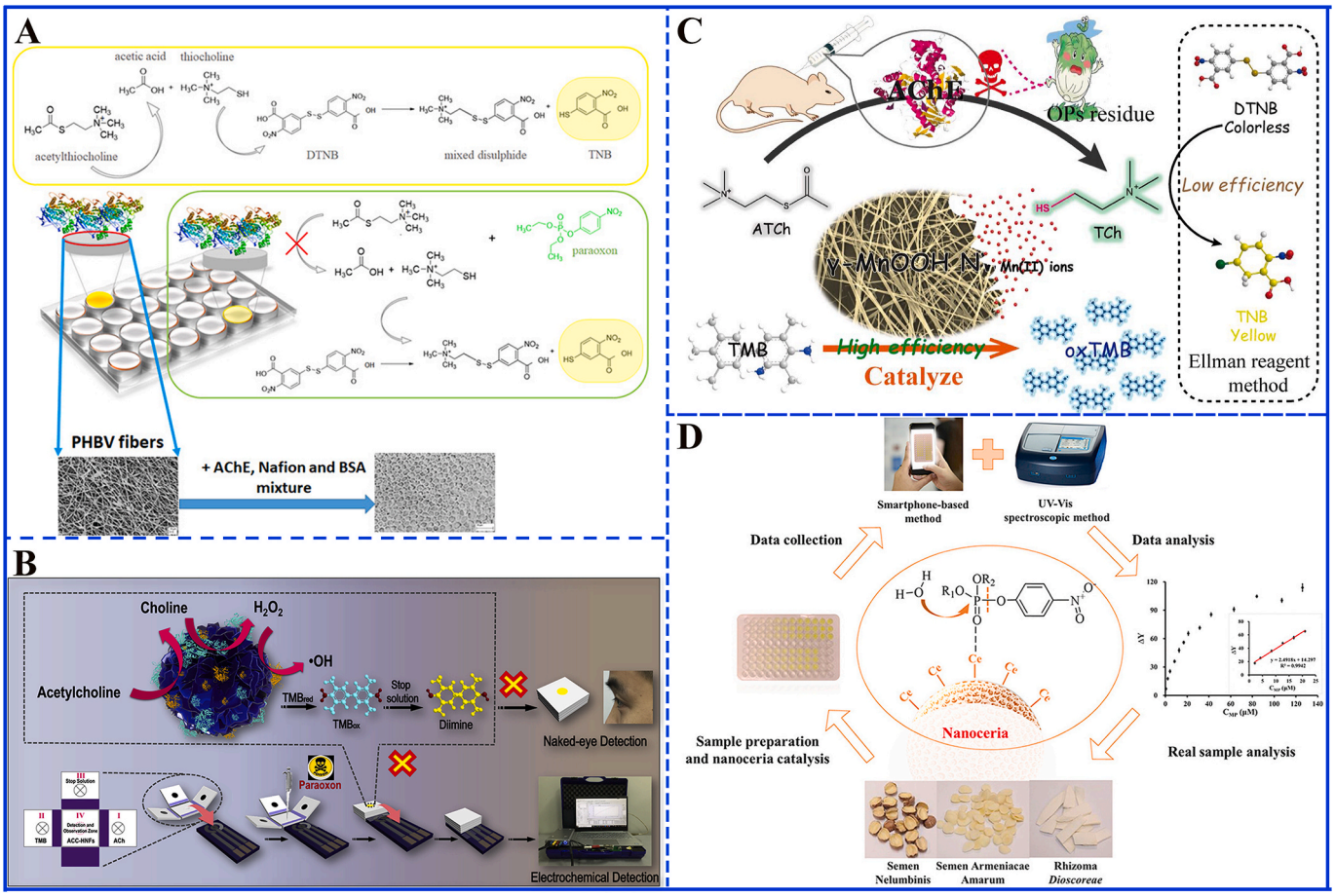

Fig. 10. Illustration of CM biosensing strategies for the assays of OPs based on chromogenic reagents as chromogenic substrate. A. Multi plated biosensing method utilizing Ellman regents DTNB as a chromogenic substrate (Reproduced with permission from Ref. [104]. Copyright 2020 Elsevier Ltd.); B. Cu-based nanoflowers utilizing as a peroxidase-like and a carrier of AChE and CHO (Reproduced with permission from Ref. [16]. Copyright 2019 Elsevier Ltd.); C. γ-MnOOH nanowires utilizing as an oxidase and TMB as a chromogenic substrate (Reproduced with permission from Ref. [112]. Copyright 2019 Elsevier Ltd.); D. Dual-mode strategy for the detection of OPs with nanoceria as a phosphohydrolase (Reproduced with permission from Ref. [116]. Copyright 2019 Elsevier Ltd.).

reagents. Jin et al. [16] fabricated a Cu-based organic-inorganic hybrid nanoflowers (HNFs) biosensor (Fig. 10B). The Cu-based HNFs could not only exhibit excellent peroxidase-like activity, which catalyzed H_2O_2 to produce •OH but also provide more active sites for more enzyme loading due to the large surface area. Furthermore, Cu-based HNFs maintained the stability of the natural enzyme and reduced leaching during recycling due to natural enzymes being absorbed into the gap of petals rather than dangling on the surface of the HNFs. In addition, Fe–N–C single atom [20], Cu–N–C single atom [107], GO [108], PtNPs [109], Fe_3O_4NPs [110], and ATCh [111]were also used as peroxidase-like in the enzyme-based CM biosensing platform for OPs detection.

Most interestingly, oxidase-like can also catalyze the oxidation of TMB to produce blue TMBox. On this basis, many novel oxidase-like-enhanced CM biosensors were successfully constructed for OPs determination. Huang et al. [112] fabricated a facile paper-based CM biosensor utilizing γ-MnOOH nanowires (NWs) as an oxidase and TMB as a chromogenic substrate for sensitive and rapid determination of OPs (Fig. 10C). The biosensing mechanism was based on the selective reaction with AChE and ATCh generated by TCh, which breaks down oxidase-like γ-MnOOH NWs into invalid Mn^{2+}, resulting in remarkable activity loss of MnOOH nanozymes towards TMB oxidation. OPs could inactivate the activity of AChE and restrain the production of TCh, thus decreasing the degradation of MnOOH NWs. Such a biosensing platform in solution state exhibited relatively low LODs for AChE activity (0.007 mU mL^{-1}), dichlorvos (0.14 ng mL^{-1}), and omethoate (0.35 ng mL^{-1}). Furthermore, the portable assembly of such an AChE-nanozyme tandem reaction performed well on the test paper, reaching LODs of 0.1 mU mL^{-1} for AChE, 3 ng mL^{-1} for dichlorvos, and 10 ng mL^{-1} for omethoate, respectively. In addition, such a CM biosensing platform not only exhibited great anti-interfere capacity, high selectivity, and worked well in real samples but also demonstrated to be ecologically sustainable with minor secondary pollution to the ecosystems. On this basis, Fe–N–C single atom [113], MnO_2 nanosheets [114], and nanoceria [115] were used as oxidase-like to fabricate CM biosensing platform for OPs detection.

Nanoceria also has the property of phosphohydrolase, which can catalyze the hydrolysis of some OPs to bright yellow *p*-nitrophenol (*p*-NP). Wei et al. [116] explored a dual-mode strategy without natural enzymes for OPs determination in real samples (Fig. 11D). The detection mechanism was that OPs could be hydrolyzed by nanoceria to bright yellow colored *p*-NP and the intensity was directly proportional with the concentration of OPs. Therefore, a dual-mode platform, including spectroscopic and smartphone-based colorimetric strategy, was proposed. Under optimal conditions, the LODs of both two were 0.42 μM for PM. This dual-mode strategy based on different mechanisms could not only meet the urgent need for on-site detection of OPs in the plant, food, and environmental samples, even those containing complex substances but also overcome the drawbacks of natural enzyme-based biosensors in harsh conditions.

Nanozyme-based CM biosensing methods have shown some advantages of portability, simplicity, practicality, and high speed. However, their detection sensitivity and accuracy are easily influenced by the

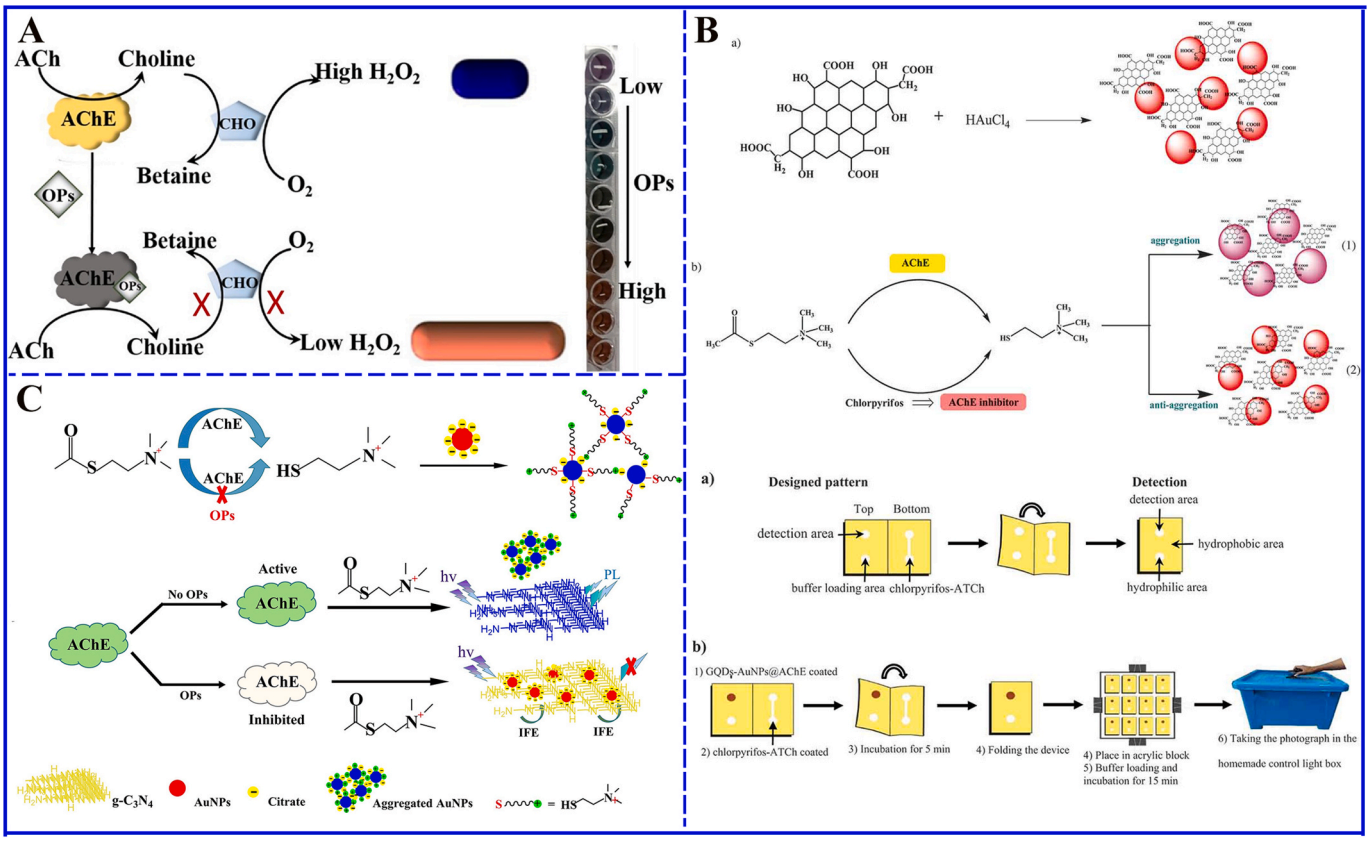

Fig. 11. Schematic illustration of CM biosensing strategies for the assays of OPs based on gold nanomaterials as chromogenic substrate. A. Biosensing system with the change in the size of AuNRs (Reproduced with permission from Ref. [120]. Copyright 2018 Elsevier Ltd.); B. 3D-μPAD biosensing platform with the change in cross-link aggregation of AuNPs (Reproduced with permission from Ref. [122]. Copyright 2019 Taylor & Francis.); C. Fluorometric and colorimetric dual-mode strategies through IFE between AuNPs and g-C_3N_4 (Reproduced with permission from Ref. [124]. Copyright 2018 Elsevier Ltd.). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

background color of samples [117].

3.4. 2. Colorimetric biosensing strategy based on gold nanomaterials as chromogenic substrates

Noble metal nanomaterials of different nature have found widespread utilization in colorimetric biosensing and bioimaging due to their strong LSPR in the visible or near-infrared wavelength range [118]. Gold nanomaterials as signal transducers have been broadly applied to construct CM biosensors for OPs determination because of their excellent catalytic, electronic, chemical, and optical properties [119]. The construction strategy of the CM biosensing method based on gold nanomaterials is mainly divided into two pathways as they exhibit different colors depending on their size and state of aggregation (Fig. 11A–C).

The first mechanism is based on the generation of H_2O_2 triggered by the ACh-AChE-CHO system, which can regulate the etching of gold nanorods (AuNRs), resulting in the corresponding change in size, LSPR band, and the color of the detection system. Liu et al. [120] constructed a multicolor biosensing platform for OPs detection based on the inhibition of AuNRs etching (Fig. 11A). The bi-enzyme cascade catalyzed ACh to H_2O_2 and triggered the etching of AuNRs, which resulted in the LSPR band shift of AuNRs accompanied by a multicolor variation. OPs restrained the activity of AChE, which restricted the generation of H_2O_2 and the etching of AuNRs. Multiple colors of AuNRs significantly improved the visual detection of OPs. Under optimum conditions, OPs were detected rapidly with a LOD of 0.32 ng mL^{-1} for demeton and 0.81 $\times$ 10^{-2} ng mL^{-1} for dichlorvos.

The second mechanism is based on the change in cross-link aggregation of AuNPs. In this mechanism, TCh, as the catalytic hydrolysates of AChE, can react with, or replace the functional groups on the surface of AuNPs, and this aggregation of nanoparticles results in a visual color variation. OPs can inhibit AChE activity, which consequently restrains the generation of TCh, resulting in the color variation of the AuNPs probe [121]. Chungchai et al. [122] constructed a three-dimensional microfluidic paper-based analytical device (3D-μPAD) with a CM biosensing platform for OPs determination in vegetable samples (Fig. 11B). The 3D-μPAD was constructed simply and cheaply by one-step polymer-screen printing, utilizing rubber latex waste as a hydrophobic reagent. The 3D-μPAD design included two sheets: a sampling sheet in the shape of a dumbbell design and a testing sheet containing two circular zones. AChE could catalyze the hydrolysis of ATCh to produce TCh, which led to the aggregation of GQDs-AuNPs and provided a purple-blue-colored solution. Incubation with chlorpyrifos restrained the activity of AChE, leading to an anti-aggregation of red-colored GQD-AuNPs. Chlorpyrifos could be determined by ImageJ, over a linear range from 1.0 to 1000 ng mL^{-1}, with a LOD of 0.7 ng mL^{-1}. This 3D-μPAD possesses excellent selectivity and sensitivity for rapid and low-cost screening OPs and promising prospects in on-site detection.

In addition, colorimetric and fluorometric dual-mode strategies were utilized for OPs detection via IFE between QDs and AuNPs [123]. Xie et al. [124] constructed a sensitive, simple, and green dual-signal detection method for OPs with AuNPs and g-C_3N_4 (Fig. 11C). AuNPs were used not only as CM probes but also as fluorescent absorbers, which could quench the FL of g-C_3N_4 through IFE. AChE catalyzed the hydrolysis of ATCh to TCh, which resulted in the aggregation of AuNPs and the recovery of FL, accompanied by a color variation from claret-red to blue. OPs restrained the activity of AChE and the aggregation of AuNPs, resulting in FL quenching. Under optimum conditions,

chlorpyrifos could be determined at a linear range of 2.0×10^{-2} - 6.0×10 nM with a LOD of 6.9×10^{-3} nM. More importantly, the biosensor showed potential applications for OPs assay in real samples.

Despite several advantages of CM biosensing strategy based on cross-link aggregate including cost-effective and easy-to-use, there are still some deficiencies, including the false negative/positive caused by the auto-aggregation of colloidal nanoparticles under the change of external environment and the limited kinds or intensity of color variations, which are not suitable for visual detection [125].

4. Conclusion and prospects

Continuous concerns on OPs residues have provided a long-driven force to explore novel techniques. Up to now, large numbers of research literature have been published for OPs detection to meet the social and market requirements. With the emergence of high affinity and recognition of enzymes, as well as various novel nanomaterials and signal transduction approaches, optical biosensors possess excellent performance to monitor OPs residues in food matrices and complex environments. In particular, the visualization and simplification design, making them perfectly suitable for on-site detection and POCT. Herein, we introduce various kinds of enzymes used as bio-recognition elements and sensing mechanisms. Then, we have reviewed a variety of optical biosensing strategies based on enzymes as recognition elements that were ingeniously designed and successfully used for OPs determination, with a specific focus on photoluminescence (PL), chemiluminescence (CL), electrochemiluminescence (ECL), and colorimetric (CM) biosensing strategies. We not only highlight the state-of-art developments and construction strategies of enzyme-based optical biosensing for OPs but also summarize the existing deficiencies of each strategy.

Although enzyme-based optical biosensor has a promising prospect in OPs detection, there are still many challenges to overcome. (a) These enzymes easily lose activity under harsh environmental conditions (e.g., harsh pH conditions, high temperature, and organic solvent), (b) enzymic regeneration is another key factor affecting its selectivity and sensitivity, and (c) the lifetime is short and their purification is quite costly and time-consuming. Apart from this, based on enzyme inhibition biosensing strategies are not selective since enzymes are inhibited by neurotoxins that include not only OPs but also carbamate pesticides and many other compounds. Thus, these tools cannot be used to quantify an individual or a class of OPs. In particular, most optical biosensors are still being tested at a laboratory level. The properties and quantities of target OPs in the samples are known in laboratories, but this is not the case for field analysis. Consequently, the results obtained in the laboratory are difficult to validate using the results obtained from the actual samples because of different conditions. It should be emphasized that the practical use of optical biosensing to monitor the residues of OPs in environmental samples is still limited, which is related to the stability, intensity, quantum yields, and lifetime of the optical signal.

To encounter these challenges, tremendous opportunities and new trends are emerging. Novel nanomaterials and technologies are promising candidates for OPs detection with optical biosensing. The immobilization of enzymes with metal-organic frameworks (MOFs) materials can not only improve the stability of the natural enzymes in a harsh environment but also increase their recyclability. However, the conjugation between recognition elements and nanomaterials will inevitably increase the cost and complexity of optical biosensors, especially suppressing the distinguishability of recognition elements. The synthesis of nanomaterials with a relatively narrow size distribution will seriously influence the performance of the sensor because the inhomogeneous distribution of nanoprobes can reduce analysis accuracy. Thus, future endeavors should focus on addressing the above obstacles. Furthermore, the application of novel nanomaterials as signal reporters, catalysts, and substrates exhibits advantages in terms of enhanced accuracy and sensitivity. In addition, the use of the μPAD omits the use of a spectrophotometer and the concentration of OPs can be easily calculated using the digital mobile phone camera and portable scanners. Therefore, POCT possesses countless potential in the field of OPs detection. The integration of nanoparticles into small nano-based chips will open the door for the "lab-on-chip" concept. It will be a promising and sensitive tool for on-site and real-time determination of residual OPs.

Declaration of competing interest

The authors declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.talanta.2021.123145.

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