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Current Advances and Prospects on Implementation of Highly Sensitive Aptamer-based Dual System for Melamine Detection: New Promising Tool of Great Affinity

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Abstract

Much attention has been devoted to melamine (MA) analysis in food products in accordance with the food safety standards. Aptamer-based analytical techniques thrived with the improvements in latest tools, analytical reagents and methods and most importantly iterative *in vitro* selection process known as systematic evolution of ligands by exponential enrichment (SELEX). Aptamer-based techniques possess very high affinity and specificity towards contaminants and play a pivotal role in MA detection. However, success depends on the starting aptamer, selection of appropriate nanoparticle, target molecule(s) and characterization of advances in aptamer selection, strategies of preparing, treating the nanoparticles analytical system methods. Current review has focused to elaborate the key recent innovation in aptamer-based dual system construction for MA detection. We have also highlighted the promising types of aptamer-conjugated nanomaterial for the specific recognition of some other potential adulterants and food hazards. Finally, we proposed future directives in developing novel aptamer and further condition optimizations that could give high-throughput food-safety analysis method and melamine "zero tolerance" towards food safety incidents.

Keywords: Aptamer; SELEX; Nanoparticles; Melamine; Detection

Abbreviations: CDC: Centers For Disease Control Prevention; Agnps: Silver Nanoparticles; TSE: Transmissible Spongiform Encephalopathy; Aunps: Gold Nanoparticles; HPLC: High-Performance Liquid Chromatography; CE: Capillary Electrophoresis; AFM: Atomic Force Microscopy; CTA: Chromotropic Acid; PDDA: Polydiallyldimethylammonium Chloride; GC: Gas Chromatography; ELISA: Enzyme-Linked Immunosorbent Assay; Haucl4: Chloroauric Acid; SELEX: Systematic Evolution of Ligands By Exponential Enrichment; LOD: Limit of Detection; STM: Scanning Tunneling Microscope; MA: Melamine; SPM: Scanning Probe Microscopy; MS: Mass Spectrometry; SPR: Surface Plasmon Resonance Assay; Prp: Prion Protein; SERS: Surface Enhanced Raman Spectroscopy; SAA: Salfanilic Acid; ELAAS: Enzyme-Linked Aptamer Assays; UTR: Untranslated Region

Introduction

Recently, melamine (MA) has become one of the major global food safety concerns being notorious for its effects on human and animal health. Owing to its water-repellent, shrink-resistant, stain-repellent and fire-retardant properties, the role of MA has gained a significant consideration in manufacturing of tableware, industrial coatings, paints, adhesives, glues paper, floor tiles, paperboard and plastic packages. It has common structure with triazine family where some of the members serve as herbicides. MA is a non-registered fertilizer in the U.S. but it is still practiced as a fertilizer in some other parts of the world [1]. In 2007, Food and Drug Administration (FDA) strictly prohibited MA as a source of non-protein nitrogen in food or feed even if it cannot solely cause side effects on animals like cats and dogs. However, when combined with its derivative cyanuric acid through gut microbiota mediation (Figure 1) (e.g. *Klebsiella terrigena*), it forms insoluble crystals in pets leading to renal failure [2]. The hallmark of kidney stones is renal colic, hematuria, little or no urine, kidney infection, and/or high blood pressure. The cases of pediatric ailments like kidney stones caused by MA has been reported in nearly 300,000 infants and deaths of six by the Pediatric Environmental Health Specialty Units (PEHSU) [3]. In 2008, the Centers for Disease Control Prevention (CDC) has also found MA in Chinese-manufactured infant formula [4]. To date, MA detection has extended beyond the milk products to meat, poultry, eggs and various vegetables. MA deposit in eggs from poultry fed with MA contaminated feed [5]. MA nitrogen content is above 65% by weight, thus it is use as food adulterant and traditional nitrogen-based tests of Kjeldahl and Dumas methods lack accuracy in discriminating between the proteinous and MA nitrogen [6]. Safety limit of MA set by UN food standard commission in food and beverages is 2.5 and 1 ppm respectively with exception of infant formula [7,8]; and this has led to search for the fast and accurate detection methods. Several analytical techniques are currently available such as fluorescence-based techniques [9], scanning probe microscopy (SPM, AFM, STM), surface enhanced raman spectroscopy (SERS) [10], electrochemical [11], surface plasmon resonance assay (SPR) [12] and impedance spectroscopy for MA [13]. Development of analytical techniques such as liquid chromatography [14], liquid chromatography-tandem mass spectrometry (LC-MS/MS) have been used for MA screening and confirmation due to their good selectivity and detection limits [15-17]. HPLC with fluorescence detection of MA [18], LC-Raman spectroscopy [19], capillary zone electrophoresis (CE) have been also utilized [20]. Despite accuracy of instrumental techniques such as HPLC, GC, and CE; they are time-consuming and

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expensive [21]. Furthermore, in detection of melamine in pet food samples, an inhibition ELISA was developed based on the monoclonal antibody that give efficient standard linear curve ranging from 0.03 to 9 ng/l with a limit of detection (LOD) 0.01 ng/ml and assay sensitivity 0.35 ng/ml [22]. However, the above mentioned techniques require more time of development and cannot be compared to aptamers-based techniques. The latter possess the ability to target molecules for which instrumental techniques and antibodies are not well suited with equal high specificity and affinity. Currently, aptamer-coupled techniques such as immunological (nano-ELAAS) [23], fluorescent chemicals (perlene) [24], nanoparticles (NPs) [25,26], electrochemical [27,28] and colorimetric aptamers [29] are available in form of biosensors. The use of nucleic acids bio-detectors '*Aptamers*' showed high ability to recognize specific targets with great affinity, stability, quick, cheap and easy to develop using SELEX [30] or automated *in vitro* selection that reduces the duration of a selection process from several weeks to three days [31]. Aptamer is derived from the Latin word "aptus" meaning "to fit" because of its strong binding to specific targets based on structural conformation. More interestingly, its combination to colorimetric nanomaterials, gives naked-eye visual detection. In this review, we have elucidated recent implementation of nanomaterial-nucleic acid (aptamers) dual system construction in bioassays to detect the infinitesimal amount of MA in foodstuffs added either non-intentionally (e.g. melamine-formaldehyde resin migration from tableware to food or beverages) or intentionally as an adulterant.

Medical Significance of Melamine

Analytical techniques for MA detection are highly needed in biomedical and clinical field due to frequent use of plastic tableware, water dispensers and other similar sources of MA. The HPLC analysis showed that 20.78% of breast milk samples contained MA levels between 10.09 and 76.43 ng/l [32]. Despite the LOD was below than that established by WHO, fast diagnosis for MA is still a significant concern to prevent the acute renal failure development (Figure 1). Continuous consumption of MA in low dose may also lead to urolithiasis and nephrolithiasis [33], hippocampal synaptic plasticity and spacial memory [34]. Currently, Yin et al. revealed the effects of MA on mice spleen lymphocytes by decreasing CD4+/CD8+ in presence or absence of MA-cyanuric acid complex formation, suggesting that MA may act as inducer and suppressor of expression of Bax and Bcl-2, respectively [35]. As a consequence of this, Aptamer and nanoparticles assay in detection of molecules such as MA, DNA and proteins may prove a new tool of detection.

Selection of Aptamer Probes

RNA has ability not only in coding for proteins but also in catalyzing reactions, binding other RNAs, proteins or specifically can bind to a target ligand(s) [30]. Aptamers are obtained from a large random sequence pool containing about 1013-1015 single-strand RNAs composed of a random sequence region flanked by a binding site. Incubation of these oligonucleotides with the single target or a large variety of targets molecule(s) results binding with high affinity and specificity in three-dimensional shape [36]. Few nucleic acids bind to the target are considered as aptamers. This step is followed by washing which help to filter out unbound nucleic acids. Aptamers are separated from the target by elution and PCR amplification of bound nucleic acids is done to create a new library. The selected sequences used in a new round of SELEX for further optimization (Figure 2). The variant SELEX exists to enhance oligonucleotides conformation stability or resistance to nucleases depending on target molecule. Some of them are genomic SELEX or cDNA-SELEX [37], photo SELEX [38], covalent-SELEX or cross-linking SELEX [39-41], multistage SELEX [42] used for starting pool rationalization or improve aptamer selectivity using negative SELEX protocol or counter SELEX, and deconvolution SELEX or subtractive SELEX. These help to remove undesirable adsorbed oligonucleotides from the poolby matrixes that used for immobilizing the targets and distinction of similar structures [43]. In addition, in order to enhance targets applicability, other variants SELEX used are: Whole bacteria-SELEX [43], blended SELEX [44], TECS-SELEX [45], complex target SELEX [46], toggle SELEX target-switching [47], expressions cassette also known as SELEX-SAGE [48], the mirror-image SELEX or Spiegelmer technology [49], whole cell-SELEX [50]. Efficacy is the prerequisite for any aptamer-based design; several SELEX strategies such as non-SELEX or NECEEM-SELEX, CE-SELEX [51], microfluidic SELEX [52], HTS-SELEX or automated SELEX [53], FluMag-SELEX [54], *in silico* SELEX [55] are applicable. However, currently improvements in SELEX have been made. For example: SELEX process needs a PCR step, the randomized region of the oligonucleotide libraries must be flanked by two fixed primers binding sequences. It has been designed an *in vitro* selection novel type of dual RNA library for mirror-image peptides detection like Ghrelin. It carries fixed sequences which constrains the oligonucleotides into a partially double-stranded structure that allows primer less selection in order to minimize the primer binding sequences to be part of the target-binding motif [56]. Moreover, DNA aptamers with only natural bases can often lack the desired specificity and binding affinity to target proteins compared to aptamers containing recombinant bases. Thus, over 100-fold affinity DNA aptamers have been developed using expanded genetic alphabet of nucleic acid (use of unnatural libraries bases). The DNA aptamer possessing the four natural nucleotides and unnatural nucleotides against two human target proteins, interferon-γ (IFN-γ) and vascular endothelial cell growth factor-165 (VEGF-165) that bind with the dissociation constant of 0.038 nM and 0.65 pM, respectively has also been developed in the same fashion [57].

For MA detection, the most commonly used aptamers are in form of poly-Ts aptamer (ssDNA) with purified sequence 5'TTTT TTTTTTTTTTTTTTTTTTTTTTTTT [58]. Yun et al. used the selected MA aptamer 5′-TTTTTTTTTTTTTTTTTTTT-3' to detect melamine in milk sample. This aptamer has potential to protect gold nanoparticles under high salt concentration conditions by averting the immediate colour change of AuNPs upon addition of MA because the latter combine competitively with aptamer [59]. Thus, the well selected aptamer shows efficiency in stabilizing nanomaterials and consequently gives accurate results (Figure 2).

Gold Nanoparticles for MA Detection

The gold, silver and quantum dots nanoparticles have emerged as new tools that ensure the food safety via providing fast and reliable detection approach for targets with simplicity, lower cost compared with immunoassay-based and chromatography based methods. Gold nanoparticles (AuNPs) are synthesized using sodium citrate reduction method [60]. This method yields particles with desired dimensions by changing the gold precursor salt and sodium citrate molar ratio. It works both as a reducing agent for nucleation of AuNPs and as stabilizing agent by coating the nanoparticles' surface and inhibiting their aggregation in solution. When MA is introduced in the system, hydrogen bonds formation between MA amine groups and citrate ions decrease the electrostatic repulsion between individual AuNPs and results in the AuNPs aggregation. The major advantages are based on the facts that no sophisticated apparatus is needed, rapid and naked-eye color change observation, giving a precise quantification of MA

when analyzed on UV-Vis spectrometer. For example, well-dispersed AuNPs solution is red, whereas aggregated AuNPs appear in blue or purple colour [61]. However, other methods of AuNPs synthesis are used because sodium citrate method provides small size nanoparticles concentration. AuNPs are synthesized from concentrated $HAuCl_4$ via addition of sodium hydroxide, pH and temperature control [62]. MA was detected using AuNPs with a LOD 0.4 mg/L displayed in 12 min including sample preparation [63]. The developed gold nanoparticle-based kit for MA detection in milk products reached working range of 1-120 mg/l improving time of detection about 10 min including sample pretreatment [64]. However, Cao et al. found that hydrogen-bonding can induce colorimetric detection of MA by label free, and nonaggregation-based AuNPs probe prepared using 3,5-dihydroxybenzoic acid (DBA) reducer interact with MA through strong hydrogen-bonding interaction. Consequently, the melamine can hinder nanoparticles generation resulting in color change from purple to yellow green with gradual increase of melamine concentration. The plasmon absorbance of the formed AuNPs allows the quantitative detection of MA with MA concentration sensitivity ranging from 1×10^{-9} M to 1×10^{-5} M, a linear coefficient of 0.993 and high selectivity to melamine with a low detection limit of 8×10^{-10} M [65]. As Media pH and reaction time are major influencing factors of AuNPs aggregation, Naveen et.al recently improved citrate reduction method [63] by preparing AuNPs with 5ml of 38.8 Mm trisodium citrate, 8.0 NaOH and further optimization in sample extraction and detection of MA. The AuNPs changes from its wine red color to blue or purple with MA detection down to a concentration of 0.05 mg/l determined by monitoring with the naked eyes or a UV-Vis spectrophotometer [66].

Although silver nanoparticles AgNPs are often used for MA detection, gold nanoparticles are more stable with less stringent requirements for storage and handling. In addition, during melamine detection, it has also been seen that AuNPs treated with citrate buffer induce highly an enhanced melamine signals in the Raman spectrum due to the formation of SERS "hot spots" caused by the ability of melamine to form AuNPs aggregates. The concentration range of 0.31-5.0 mg/l in milk with a limit of detection of 0.17 mg/l has been obtained in lower than 30 minutes [67]. Even though it improved time of detection, its LOD is of concern.

Silver Nanoparticles for MA Detection

Silver nanoparticles (AgNPs) can be prepared using borohydride reduction method [68], but some modifications improved the efficiency. Its detection principle consists of the ability of AgNPs to be stabilized and coated in aqueous solution with negatively-charged citrate ions [69] able to interact via Van der Waals' force and with the positively-charged MA to its three exocyclic amine group and a three-nitrogen hybrid ring. This means, when MA is added to a solution of AgNPs, attachment occurs with result of AgNPs aggregation followed by color change. It is thought that either three exocyclic amine group or a three-nitrogen hybrid ring results the label free AgNPs aggregation [70]. Compared with gold nanoparticles, AgNPs have some advantages, such as lower cost of preparation, higher extinction coefficients relative to AuNPs of the same size. Therefore, they are used as calorimetric probes of MA detection and other hazards to assure food safety and protect public health. Despite some advantages of Ag NPs over AuNPs, several papers proposed AuNPs as preferred substrates for melamine detection since the color of the particles changes after the MA-AuNPs interaction in solution. The use of label-free AgNPs detection of MA concentration in raw milk pretreated with chloroform and trichloroacetic acid to remove the protein and fat resulted a naked eye or a UV-Vis spectrophotometer yellow to red visible color change with detection limit of 2.32 μM~0.29 mg/l, which is below the safety limit of 2.5 ppm recommended in USA and EU. Whereas for infant formula in China, only 1 ppm of MA is tolerated, thus it has an advantage over some methods used for MA detection but not conducive as AuNPs [71]. However, in one way, this method can be interfered by some amino acids and other positively charged molecules that can give false positive results due to some instability of prepared AgNPs. In another way, no MA-cyanuric acid aggregation, that can thus show no color display. Therefore, chromotropic acid (CTA) capping of AgNPs makes them to remain in stable and dispersed form. Once MA is added in nanomaterials solution, it will bind with CTA found on the CTA-AgNPs complex through hydrogen bonding with high selectivity to its structural analogs like cyanulic acid. MA only can act as hydrogen donor to sulfur- groups of the CTA-capped AgNPs and thus induces aggregation accompanied by yellow to orange color change observed by naked eyes [72]. However, it is still require a method for detection of MA in food and beverages with high sensitivity. Thus, the same group of Fangying developed an AgNPs conjugated with sulfanilic acid (SAA), this combination of techniques significantly increased the sensitivity and selectivity of melamine in pretreated milk and only can melamine react with SAA-AgNPs followed by rapid aggregation due to the MA affinity towards the SAA functional groups. The selectivity of this method is below 50 nM and LOD of 10.6 nM which is not only low compared to the multiple existing methods used to detect MA, but also cheap with one sample treatment with analysis costs of 0.5$ [73]. However, further meticulous research with an easy, cost-effective method lies ahead to achieve ultrasensitive and selective methods for screening MA level in food products. In the next section, we have focused on the aptamer-nanomaterial techniques and different treatment strategies as a potential solution to nanoparticles drawbacks mentioned above.

Aptamer-Conjugated Nanoparticle Based Novel System for MA Detection

Aptamer-modified AuNPs show high stability and selectivity compared to unmodified AuNPs in MA and other small molecules sensing [74]. Either ssDNA or RNA aptamers are used to label nanoparticles in the synthesis of dual system aptamer-NP probe for MA detection. The probe is stabilized at pH 6.6 or 7.0 NaH_2PO_4-

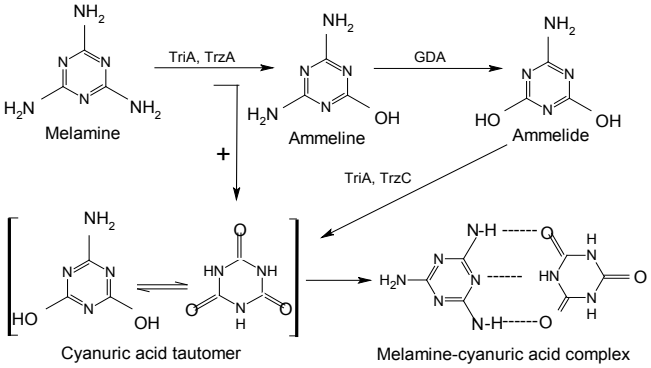

Figure 1: Melamine combined with its derivative product cyanuric acid to form melamine-cyanuric acid insoluble crystal complex that can cause renal failure (kidney stones, hematuria, high blood pressure etc.). This figure also depicts the gut microbiota mediation of enzymatic conversion of melamine to cyanuric acid. TriA stands for melamine deaminase, TrzA for S-trizine hydrolase, GD for Guanine deaminase, AtzC for n-isopropylammelide aminohydrolase and TrzC for Ammelide hydrolase.

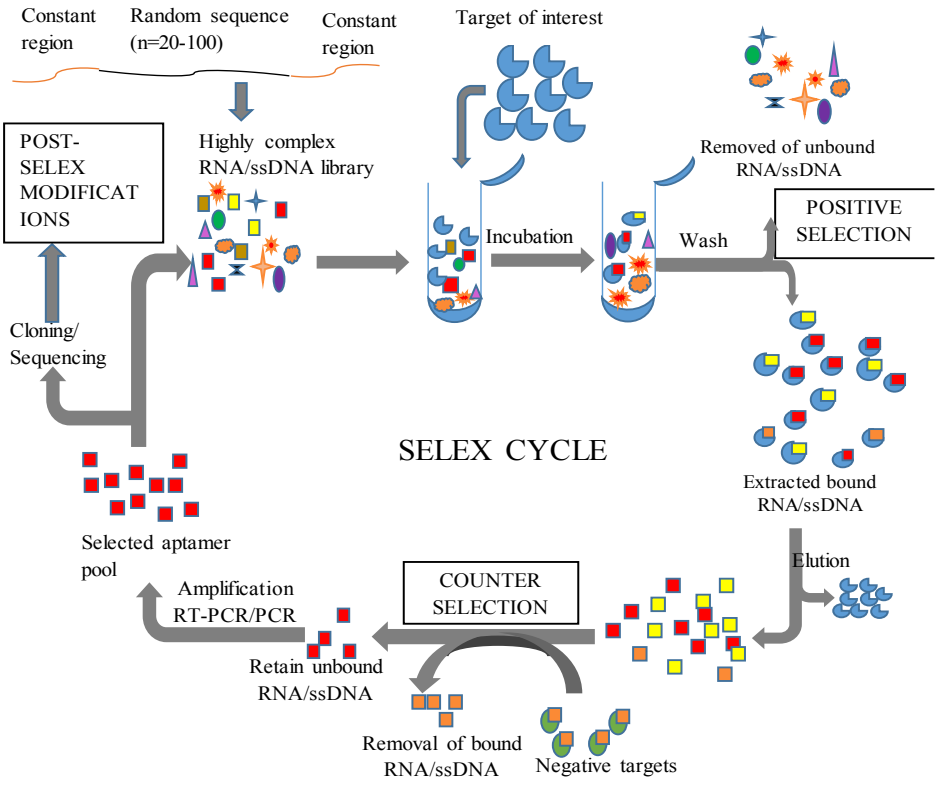

Figure 2: General principle of SELEX.

Na_2HPO_4 buffer solutions and in high concentrated electrolyte like 25-35 mmol/l of NaCl solution. High salt concentration neutralizes free negative charges of citrate when chloroauric acid ($HAuCl_4$) is used for AuNPs synthesis that leads to the AuNPs aggregation. Upon addition of MA, MA-aptamer-modified AgNP complex is formed that can result an increase of resonance scattering at 470 nm with a linear relation to added MA concentration [75]. The increase of MA decreases the unreacted NGssDNA and the RRS intensity decrease linearly accompanied by color changes from red to blue. While using this method in MA detection, the results ranged between 1.89-81.89 µg/l with LOD 0.98 µg/l determined by the NGssDNA probe [58]. For label free MA aptasensor, the AuNPs are incubated with anti-MA aptamer for 15 min followed by purification using centrifugation at 10,000 rpm for 5 min to obtain the aptamer-protected AuNPs. The salt concentration also influences results (Figure 3). The salt tolerance of aptamer-protected AuNPs should be tested using NaCl solutions at different concentrations. Initially, the higher concentration of salt solution results in the higher sensitivity. Conversely, it decreases the stability of intra-assay and the productivity of sensing system. Thus, the optimal concentration of 15 mM NaCl was adopted to induce the AuNPs aggregation and assure sensitivity. AuNPs should be treated because untreated ones show no color change after binding the target. However, this pretreatment doesn't intervene in detection optimization [76]. Intriguingly, while adding aptamer to AuNPs, there is no change in surface SPR absorption peak and stays 520 nm at UV-VIS spectra. By contrast, upon adding MA into AuNPs-aptamer solution the SPR absorbance 520 nm decreases up to 620 nm followed by color change from red wine to blue visible by naked eye or UV-VIS spectroscopy. Furthermore, it is important to take into account that the reason of color change is still surmised that the addition of a target results to the aggregation of AuNPs due to competitive binding of MA to aptamer (Figure 3). Compared to bare nanoparticles used in MA detection illustrated above such as AuNPS [63] and AgNPs [70], this method promises the reliability, accuracy and detection time of MA in milk samples because aptamer has ability to stabilize NPs in salts. In addition, the LOD of this method possesses same range of that LOD reported for biosphenol detection in water samples [77]. However, its LOD is lower probably due to the complexity of milk composition which may affect the sensitivity of target induced-AuNPs aggregation (Figure 3).

Based on colorimetric detection, the aptamer modified AuNPs probe was reported as an easy, quick, stable and selective method for MA in milk with LOD 4.2 µg/l. Aptamers can adsorb on AuNPs surface via electrostatic forces and react with poly-diallyldimethylammonium chloride (PDDA) that prevents AuNPs aggregation. Principles of detection consist of forming MA-aptamer complex via hydrogen bonds upon addition of MA in solution and this results the change of color due to the formation of cationic polymer which can aggregate AuNPs. The produced color can be seen with naked eye without quantitative results or measured by UV-Vis spectrum [74]. However, the degree of errors can occur due to foreign substances interference or poor manipulation.

Merits of Aptamer-Based Techniques

Nanoparticles and aptamers have remarkable features of binding with analytes due to their strong localized surface plasmon resonance and high selectivity, respectively. In MA detection, these techniques and

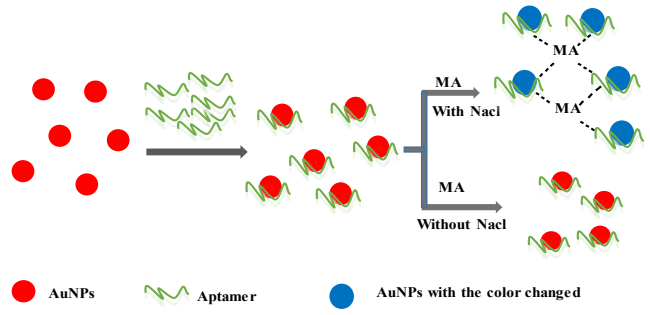

Figure 3: A schematic depicting melamine detection principle using salt mediated aptamer-NPs dual system.

their combination are efficient. Comparing current research on UPLC and HPLC, MA analysis reached a concentration of 2.59 µg/kg using the molecular imprinted solid-phase extraction-UPLC and applied as a specific sorbent for the selective solid phase extraction of MA and its metabolites [10]. However, sample preparation, instrumentation and validation of the experiment require FTIR, NMR and/or other sophisticated techniques.

Compared to newly developed ELISA and recombinant ELISA, their detection limit ranges from 0.5-7.0 µg/ml [78] which is higher than those of highest aptamer-based techniques (Table 1). However, this technique can be interfered by sample matrix and also related chemical compounds, thus possibility of false results may exist. Moreover, production of monoclonal antibody for target(s) generally has several inherent limitations *in vivo* such as: lack of MA immunogenicity due to non- recognition by the host (only proteins and few carbohydrates have the ability to induce immune response). However, Lin et al . have developed a disclose method of producing immunogens by polymerization of non-immunogens. These methods are specific for haptens with amine and carboxylic groups including MA. Crosslinking reagents have been used to polymerize those functional groups into macromolecules to obtain haptenic polymers which will be used to immunize animal for antibodies production. The non-immunogenic MA has been polymerized using glutaraldehyde to reach a preferred complete antigen size at least of 4 kDa [78,79]. However, *in vivo* produced antibodies still have experimental limitations in their applications, mainly non-specific binding that can lead to cross-reactivity and high background. Therefore, aptamers-recombinant antibody can be made using library methods instead of animal immunization technologies. Additional advantages of aptamers over antibodies include easy storage, transport, suitability in variable conditions, and stability in changeable kinetic parameters, reporter molecules and high discrimination of targets. Therefore, aptamer-NPs system is a fast and more versatile approach (Table 1).

Application of Aptamer in Food Safety

As a new platform technology, aptamer-based techniques bioassay has recently been adopted in food analysis, clinical, medical and environmental monitoring [80-85]. In food safety monitoring, aptamers are applied for detection of chemical and/or biological hazards. Illegal additives used in food adulteration such as 17-β estradiol and bisphenol A were detected using DNA aptamers5'-GGGCCGTTCGAACACGAGCATGCCGGTGGGTGGTCAGGTGGGATA GCGT-3' and 5'-TCCGCGAATTACACGCAGAGGTAGCGGCTCTGCGCATTCAATTGCTG-3' combined with 5'-CGCGCTGAAGCGCGGAAGC-3', respectively [77,86,87]. This method is based on competitive recognition of bisphenol with immobilized aptamer fixedon the surface of the electrode. MA detection in milk using ssDNA aptamer with sequence of 5'-TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT-3' [58] is highly effective. Aptamer detection and identification for various harmful microorganisms in clinical practice such as *Pseudomonas sp.* [88], *Campylobacter* sp. [89], *Escherichia coli* O157: H7 [90], *Staphylococcus* sp. [91], *Listeria* sp., and *Salmonella* sp. are also available [92,93]. Aptamers 5'-TTTGGTCCTTGTCTT ATGTCCAGAATGCTATGGCGGCGTCACCCGACGGG-3' and 5'-GACTTGAATTATACA GATTTCTCCTACTGGGATAGGTGGATTAT-3' sequences were used in salmonella serovars detection and showed high detection affinity. The aptamer S8-7 has been used as a ligand for magnetic capture of serially diluted *Salmonella typhimurium* species by detecting the whole cell content in a 290 µl sample volume containing 10^2-10^3 CFU equivalents of *Salmonella typhimurium* which resulted in relatively high binding affinity to the target with an apparent dissociation of 1.73 ± 0.54 µM [94]. Traditionally, *Salmonella* genera detection in food requires standard culture methods which include sequential steps of pre-enrichment, selective enrichment and selective differential plating. All these steps are tedious and time consuming. For decades, toxins became problematic to food safety and aptamer based techniques have been developed for the detection of toxin like Ochratoxin A with DNA aptamer [95]. Currently, Ochratoxin A has also been detected using electrochemical aptasensor [96], aflatoxins [97-100], neurotoxins [101] such as botulinum [102,103], antibiotics [104-107] as well as pesticides such as nitenpyram, chlorpyrifos and imidacloprid [108].

Conclusion and Future Directives

Aptamer, nanoparticle or aptamer-modified NPs showed efficiency in detection of MA in food or beverages with a sensitivity of 1.89-81.89 µg/l and 0.98 µg/l in short time [58]. However, AuNPs by SERS showed the concentration range of 0.31-5.0 mg/l in milk with a limit of detection of 0.17 mg/l within 30 min by improving time of detection but its LOD is of anxiety. These achievements are due to three major aspects: a) development of new aptamer-based analytical methods, b) modification in nanoparticles treatment and c) combination of techniques. To date many workers use aptamers for protecting and stabilizing nanoparticles. So far, the improved SELEX protocol is the promising tool for the detection of various target analytes, but it is still under continuous evolution. Theoretically, SELEX protocol is used in target analytes screening, but the market is still dominated by antibody-based method. This is due to two major reasons: 1) development of sensitive and specific aptamer for specific categories of target analytes is still limited and 2) limitations in further SELEX technology in order to produce efficient and low cost aptamer. In addition, it should be kept in mind that many of the above mentioned aptamer-based techniques are conceptual in that much works need to be done before practical application, even though it showed more stability in salts compared to techniques that use bare nanoparticles. Although aptamer-conjugated nanomaterials are emerging as promising platform for MA detection, much works remain in development of other aptamer-based methods because natural and modified natural nucleotides used during aptamers production often lack specificity and desired binding affinity. Thus, we propose aptamers development using expanded genetic code whereby natural and unnatural bases can be mixed and optimized for MA detection. Moreover, other tasks are to be done in investigating aptamer-NPs array-based, discovering combinatorial techniques beyond two as mentioned in detection of *Salmonella typhimurium* using nano-ELAAS (gold nanoparticles, ELISA and aptamer) [23] and developing relevant kits could curtail the time, errors and elucidate

Technique	Type of Food	Sensitivity	LOD	Reference
HPLC	Milk	0.05-10.0 µg/ml	8.1 µg/l	[109]
	Edible plants	-	2.51 µg/kg	[17]
GC-MS	Milk	-	0.01 mg/kg	[110]
	Eggs		10 µg/kg	[102]
LC-MS	Eggs	-	8 µg /kg	[15,111]
UPLC-MS/MS	Eggs	-	5-10 µg/kg	[102]
ELISA	Milk, Milk products and animal feeds		5.210-5.460 µg /l	[79,112]
ELISA KITS	Milk, milk products and animal feeds	-	1.908,2.125,4.15 µg /l	[112]
Bare AuNPs	Milk	0.31-5.0 mg/l	0.17 mg/l	[66,113]
Bare AuNPs Kit	Milk products	1-120 mg/l	-	[64]
Bare AgNPs	Milk	2.32-0.29 µg/l	-	[70,73]
Bare Aptamer	Milk	0.2 to 24 µg/l	10.08 µg/l	[114]
AuNPs-Aptamer	Milk	1.89-81.89 µg/l	0.98 µg/l	[58,59]
AgNPs-Aptamer	Milk	6.3403.6 µg/l	1.2 µg/l	[115]
SAA-AgNPs	Milk	0.1-3.1 µM	10.6 nM	[73]
CTA-AgNPs	Milk	126 µg/l	4.5 µg/l	[72]

Table 1: Recent reports on MA detection in food samples.

some obstacles like interference of other compounds towards high throughput detection of MA and other targets in food stuff.

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