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Application of DNA sequences in anti-counterfeiting: Current progress and challenges

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ABSTRACT

Counterfeiting has never been more challenging than during the COVID-19 pandemic as counterfeit test kits and therapeutics have been discovered in the market. Current anti-counterfeiting labels have weaknesses: they can either be duplicated easily, are expensive or ill-suited for the existing complex supply chains. While RFID tags provide for an excellent alternative to current anti-counterfeiting methods, they can prove to be expensive and other routes involving nanomaterials can be difficult to encrypt. A DNA based anticounterfeiting system has significant advantages such as relative ease of synthesis and vast data storage abilities, along with great potential in encryption. Although DNA is equipped with such beneficial properties, major challenges that limit its real-world anti-counterfeiting applications include protection in harsh environments, rapid inexpensive sequence determination, and its attachment to products. This review elaborates the current progress of DNA based anti-counterfeiting systems and identifies technological gaps that need to be filled for its practical application. Progress made on addressing the primary challenges associated with the use of DNA, and potential solutions are discussed.

1. Introduction

As globalization increases, the issue of counterfeit consumer goods has become more important to address. The direct effects of this illegal operation include huge financial losses, unemployment, poor health and deaths of individuals across the world (Deisingh, 2005; Sullivan and Wilson, 2017). Practically, all industries are significantly affected by counterfeiting of their products. The list includes, but is not limited to, clothing, electronics, watches, medical equipment, recreational gear and more importantly pharmaceuticals and food products (Tian, 2016; Sorak et al., 2012). Of immediate and growing concerns are that the COVID-19 pandemic has led to a surge in fraudulent activity (Customs and Protection, 2020). Counterfeiters are fooling consumers into buying fake masks, medicines, and medical equipment (International Trademark Association, 2020). The U.S. Customs and Border Protection (CBP) officers intercepted a package containing suspected counterfeit COVID-19 test kits in March 2020 (U.S. Customs and Border Protection, 2020).

The Organization for Economic Cooperation and Development has estimated that financial losses due to counterfeiting amounted to more than 250 Billion USD back in 2007 (Fink et al., 2015). According to a report published by PricewaterhouseCoopers (PwC), European € 1594 Billion could be attributed to the act of counterfeiting in 2010 (Peter

Behner et al., 2017). Counterfeit goods form a significant part of the global trade and need to be curtailed (Chaudhry and Zimmerman, 2013). The International Chamber of Commerce projects that counterfeiting and piracy can lead to losses worth 4.3 Trillion USD by 2022. A grave consequence of this act being the risk it poses to 5.4 million authorized jobs in the United States alone (Economics, 2022). It is important to note that with the advent of online trading, it is difficult to thoroughly estimate the financial losses which can be attributed to counterfeiting. With losses well above 600 Billion USD a year, counterfeit and falsified medicines form a significant part of this nexus (Lee, 2017). A direct result of the falsified and counterfeit medicines is on the well-being of consumers as such drugs with incorrect Active Pharmaceutical Ingredient (API) can pose a significant health risk (Fernandez, 2015).

A recently published report suggested that among a few Southeast Asian and Sub Saharan countries, more than one third of anti-malarial drugs were found to be falsified (Nayyar et al., 2012). Enough evidence exists to prove the detrimental effects of counterfeit drugs (Mackey and Liang, 2011) stressing on the importance of their eradication from markets. A recent example includes counterfeit benzodiazepines belonging to Teva-brand where etizolam, an analogue of benzodiazepine was used as an Active Pharmaceutical Ingredient. The

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product was being manufactured and distributed on a large scale selling over 2 million illicit pills (Jurásek et al., 2020).

The threat of counterfeiting of pharmaceuticals is well recognized and various anti-counterfeiting techniques have been proposed as the optimal solutions. While laboratory-based verification techniques can confirm the presence of counterfeit medicine, effective strategies that prevent entry of falsified products into the market are highly desirable. Some of these strategies include holograms, Quick Responsive codes, Radio Frequency Identification Tags, nanoparticles, and Deoxyribose Nucleic Acid based systems. While these techniques have been tried and tested, a DNA based anticounterfeiting system has some unique properties which are note-worthy (Wolfrum and Josten, 2005). Some distinctive characteristics of a DNA based anticounterfeiting system include higher data storage capacity and relative ease of synthesis, among others. However, a DNA based system, like others mentioned, also relies on a deterministic approach and is therefore cloneable (Arppe and Sørensen, 2017).

The aim of this review is to elaborate on the current state of DNA based anti-counterfeiting and how it compares with other emerging technologies. Primary advantages with the use of DNA for anti-counterfeiting, its major challenges, and recent developments to address them are discussed. Technological gaps that prevent the commercial application of this technology are identified.

2. Recent advances in anti-counterfeiting technologies:

2.1. Current anti-counterfeiting methods applied to pharmaceuticals.

Various analytical methods are currently used to confirm the presence of counterfeit drugs. Some of these include chromatography and spectrometry-based techniques. Mohammad et al., for example, analyzed aspirin, prasugrel, and clopidogrel in pharmaceutical and herbal products using Thin Layer Chromatography and Mass Spectrometry (Mohammad et al., 2020). Toth et al., used a Liquid Chromatography based method to detect the presence of impurities in dapoxetine, the technique was also tested on commercial tablets (Tóth, 2020). While these approaches can successfully confirm the presence of counterfeit products, they can destroy samples and may not be the best approaches for rapid evaluation of authenticity.

Spectroscopy based approaches have found an important place in analysis of pharmaceutical products owing to their non-destructive sampling procedures. Rodionova and co-workers, for example, used Near Infrared Spectroscopy (NIR) to analyze capsules in blister packs (Rodionova et al., 2018). They collected NIR spectra through the polyvinylchloride blister confirming non-destructive spectroscopic analysis of fluconazole capsules. Further, portable versions of various spectroscopy-based instruments are widely available. Tobias et al., for example, used drug checking to identify counterfeit alprazolam tablets from unregulated drug market in British Columbia, Canada (Tobias et al., 2020). Point of care FT-IR was initially used for detection of counterfeits following which the samples were analyzed using chromatography. Hand-held Raman spectrometers have also been used elsewhere to identify tablets that are not authentic (Lanzarotta, 2020; Dégardin et al., 2017). While all the stated techniques can confirm the presence of illicit pharmaceutical products, equipment required for such analyses may be expensive. Equipping points of sale with such sophisticated instrumentation can prove to be a challenge.

As pointed by Dégardin et al., analysis of packaging of a pharmaceutical product can be important in determining its authenticity. They proposed both visual inspection and sophisticated techniques such as electron microscopy and spectroscopy-based methods (Dégardin et al., 2018). Elsewhere, the packaging of vials of protein-based medicine was analyzed using both visual and analytical methods (Dégardin et al., 2019). Although visual inspection is a quick test for product authenticity, advancements in printing technologies has led to insignificant differences between genuine and illicit products. Authentication tags

that can go onto product packaging and do not lead to significant changes in traditional verification protocols offer a desirable solution. The sections below elaborate on novel sophisticated technologies that can serve this purpose.

2.2. Blockchain and IOT based platforms.

Blockchain is a relatively new technology that is gaining significant attention for various purposes and has shown great potential for pharmaceutical anticounterfeiting applications. Blockchain can ideally be defined as an open ledger that can record transactions in a verifiable manner (Alzaharani and Bulusu, 2018). Of its many applications is also monitoring movement of goods where transport from one point in the supply chain to another is recorded as a transaction. Once initiated, introduction of a counterfeit product or its deviation from a defined geographical route can be easily tracked and recorded in the information associated with the product.

In a recent study, Sylim et al., developed a surveillance system for falsified and substandard drugs and tested it in a simulated environment (Sylim et al., 2018). Abbas and coworkers further combined a blockchain based approach with machine learning which uses public reviews to make recommendations for authentic pharmaceutical products (Abbas et al., 2020). Elsewhere, blockchain technology was combined with an Internet of Things platform to develop a system that allows prevention of counterfeiting and temperature monitoring of pharmaceutical products (Singh et al., 2020). While such blockchain based approaches can offer reliable solutions to the problem of counterfeiting, this technology has its own disadvantages.

A major drawback of the Blockchain technology is the requirement of internet connectivity which may not be ubiquitous, significantly limiting its application in regions with low resources. Verification with an electronic ledger is necessary and implementation of this technology would also require a sophisticated digital infrastructure that can prove to be expensive, as was pointed out by Mori et al., (Di Francesco Maesa and Mori, 2020).

2.3. RFID and Nanoparticles

Traditional methods such as bar codes, QR codes and holograms are well established and have been fully integrated with supply chains. While simple, inexpensive, and suitable, these methods are easily cloneable and encryption is restricted to access of printing technology, as has been pointed out earlier (Arppe and Sørensen, 2017; Sung et al., 2015). Novel technologies that can address these disadvantages while maintaining affordability, and integration with supply chains are therefore desirable.

Among the current promising anti-counterfeiting technologies are Radio Frequency Identification (RFID) tags. RFID is a widely accepted method for the protection of valuable products from the web of counterfeiting. This tag consists of a microchip with unique information which can be processed using a reader. RFID tags have seen a widespread acceptance and manufacture at a commercial level as they can be integrated with complex supply chains (Wang et al., 2019). One of the primary advantages of RFID is the rapid scanning of labels which allows reading of the whole inventory shelf by shelf. Unfortunately however, it is possible to clone this tag (Cole and Ranasinghe, 2008), a major disadvantage of this technology for anti-counterfeiting applications. Cloning of RFID is achieved using replay attacks. A replay attack is the one in which the communication between the tag and its reader is recorded by a third party. This recorded information can now be used to replicate the tag, decreasing the level of security (Devadas et al., 2008). Although routes to protect the information exist (Neve et al., 2003), such measures will lead to a direct increase in costs of tag fabrication. For important commercial products, the tag is usually made a part of package label which may be removed by counterfeiters, therefore labelling of the products with an additional tag may be required.

More recently, nanotechnology is being considered to serve the purpose of anti-counterfeiting and anti-piracy. In numerous studies, nanometer sized particles in their various forms have been used as tags to serve this purpose. Campos-Cuerva and co-workers proposed the use of silver, gold and magnetic nanoparticles in varying combinations for their use as screen printable anti-counterfeiting ink (Campos-Cuerva, 2016). Elsewhere, Meruga and group used lanthanide doped nanoparticles which can provide enhanced security and can be read using a Near Infrared reader (Meruga et al., 2012). Lanthanide doped nanoparticles fall under the category of up conversion nanoparticles which exhibit a property where photons are generated with wavelengths shorter than that of the incident light (Liu et al., 2015). Some up conversion nanoparticles also have a size dependent luminescence which may be exploited to serve the purpose of detecting authentic products (You, 2016). Multiple attempts have also been made to combine the impressive properties of nanoparticles with other materials to be printed as Quick Responsive codes (Meruga et al., 2012; You, 2016; Han, 2012), adding to another layer of security. Although the beneficial characteristics of nanoparticles cannot be dismissed, it would not be easy to encrypt them as multiple nanoparticles will have to be used (Sun, 2017).

Physical Unclonable Functions (PUF) may be the most efficient route for anticounterfeiting measures as they rely on a stochastic approach due to which they cannot be duplicated. Some examples of PUF include printed random dot patterns, nanoparticles and quantum dots among others (Liu, 2019; Li, 2021). Apart from being unclonable, PUF's may be read using smartphone-based devices, this has been demonstrated in literature and remarkable encoding capacities as high as 2.5×10^{120} have been achieved (Arppe-Tabbara et al., 2019). Carro-Temboury and coworkers used multiple lanthanide based materials and devised an optical system that makes use of digitized readouts which could be compared for authenticity (Carro-Temboury et al., 2018). Further, PUF based technology can be inexpensive, although its commercial application is still in its infancy.

While a DNA based system can synthesize unique anticounterfeiting tags, it still relies on a deterministic approach and may not be able to compete with a PUF based system. Although cloneable, such a system can offer advantages such as relative ease of synthesis and encryption. Table 1 compares various anti-counterfeiting technologies and their commercial feasibility. The sections that follow discuss advantages, issues, and challenges with the use of DNA for anticounterfeiting applications.

3. DNA for Anti-counterfeiting

3.1. Primary advantages with the use of DNA

The Deoxyribonucleic acid (DNA) consists of four different bases (adenine, guanine, thymine, and cytosine) which are arranged in varying combinations to form the genetic basis of all biological organisms. With the advancements in the realm of biotechnology, and molecular biology in general, it is possible to synthesize these bases arranged in a known specific order (Aquino de Muro and Rapley, 2001). These DNA

bases can be arranged in a unique combination for anti-counterfeiting applications and can be encrypted for enhanced security. Data encryption using DNA has been well established in literature employing techniques such as cryptography (Xiao et al., 2006; Gehani et al., 2004). Clelland and coworkers for example, proposed a scheme where authenticity can be established using the encoding rule and correct primers (Clelland et al., 1999). Lieber et al., have proposed DNA stenography for the encryption of the information stored in DNA molecules, based on DNA binary strands (Hahm and Lieber, 2004). Such diverse applications work in favor of a DNA based anti-counterfeiting system. Further, a short sequence of DNA, barely 20-25 bases long, can be arranged in more than a billion different combinations as pointed by Wolfrum and group (Wolfrum and Josten, 2005).

Apart from ease of encryption, DNA is also equipped with high information density allowing storage of petabytes of data in a single gram (Erllich and Zielinski, 2017). Theoretically, as noted by Church et al., each nucleotide can code for 2 bits resulting in 455 exabytes per gram of single stranded DNA (Church et al., 2012). High information density and small size of DNA favor its use in anti-counterfeiting applications as invisible tags. A primary advantage of using DNA as authentication labels is their difficulty in being replicated. Traditional techniques that can be used to determine the sequence of DNA include sanger sequencing and its various modifications. Apart from being expensive, these techniques require trained personnel with a specific skillset that may be difficult to acquire, working in favor of its anti-counterfeiting prospects. While there is a great potential in storing data in DNA, a challenge lies in reading it as advanced techniques such as sequencing may be required (Gupta and Singh, 2013). Current methods that are used to determine the DNA sequence can span several hours, limiting its practical application. Further, while replication of DNA sequences is difficult, it is not impossible when correct pairs of primers are available. Combining DNA with other technologies such as nanoparticles and RFID can prove to be advantageous where immediate verification using RFID is followed by sequencing based product authentication (Puddu et al., 2014; Chien, 2006).

Figure 1. (a) describes major advantages with the use of DNA for anti-counterfeiting applications which include the possibility of its conjugation with other anti-counterfeiting technologies. As will be discussed further, DNA may directly be combined with traditional printing ink which may then be used to print bar codes and QR codes, offering a higher level of security (Hashiyada, 2004). Synthesis of fluorescent invisible DNA ink has also been described in literature which can be printed using traditional means (Liu et al., 2017). DNA may also be combined with Blockchain and its sequence made a part of product information enhancing product security. This combination also caters to the need of physical verification for product authenticity in the absence of internet connectivity and has been proposed by Alocilja et al. (2018).

While high information density, invisible nature, ease of encryption and conjugation with other technologies offer DNA based anti-counterfeiting system precedence over other routes, some major challenges remain unaddressed (Figure 1. (b)). Primary obstacles to the applicability of a DNA based anti-counterfeiting system include its

Table 1

Comparison of a few anti-counterfeiting technologies. Some of their important characteristics for product security are described.

Technology	Time for verification	Information Density	Replicability	Mode of Verification	Level of Encryption
Bar code/QR code	Low (seconds) (Tarjan et al., 2014)	Low-Moderate (Chiang et al., 2013)	Easy	Real time (Lin et al., 2015)	Low
RFID	Low (seconds) (Mladineo et al., 2017)	High (Vena et al., 2012)	Difficult (Devadas et al., 2008)	Real time (Wang et al., 2019)	High (Ateniese et al., 2005)
Nanoparticles	Low (seconds) (Tarjan et al., 2014)	Low	Difficult (Campos-Cuerva, 2016)	Real time/ Delayed (You, 2016; Campos-Cuerva, 2016)	Low (Arppe and Sørensen, 2017)
PUF	Low (seconds) (Arppe-Tabbara et al., 2019)	Very High (Carro-Temboury et al., 2018)	Unobtainable (Arppe-Tabbara et al., 2019)	Real time (Arppe-Tabbara et al., 2019)	Very High (Arppe and Sørensen, 2017)
DNA	High (hours) (Liu et al., 2017)	Very High (Church et al., 2012)	Very Difficult (Hashiyada, 2004)	Delayed (Liu et al., 2017)	Low

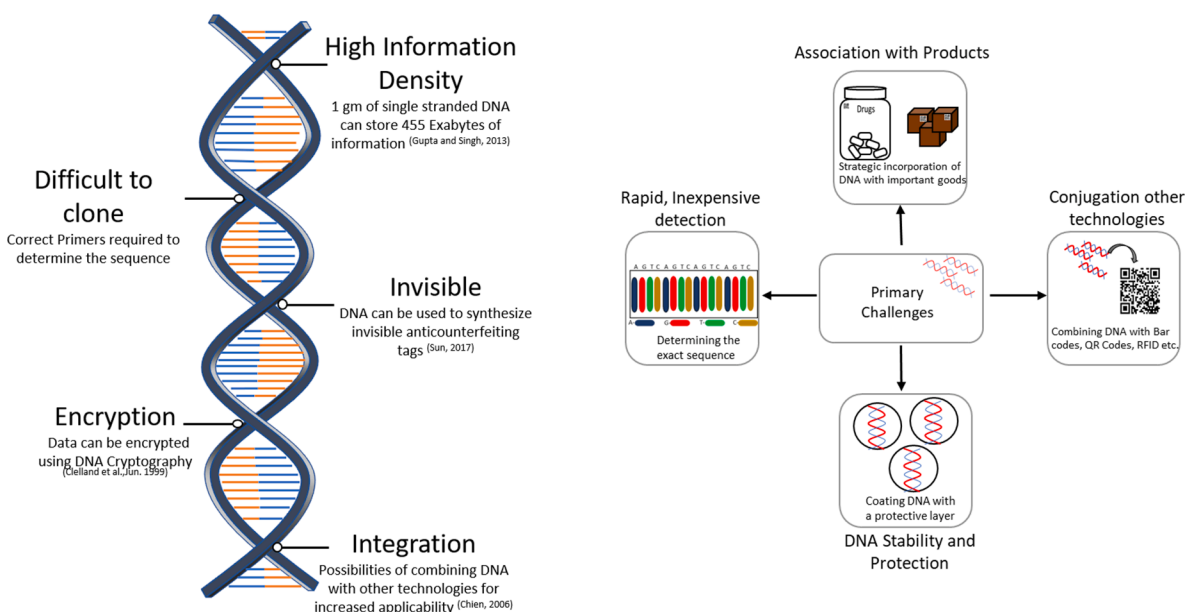


Fig. 1. (a) Primary advantages with using DNA for anti-counterfeiting applications and (b) Major challenges with the use of DNA for anti-counterfeiting.

protection in harsh environments as well as rapid and inexpensive sequence determination. These, along with logistics of its association with target products are discussed in detail in the following section.

3.2. Major Challenges with the use of DNA for Anti-counterfeiting applications

3.2.1. DNA stability and protection

Among the challenges in the use of DNA as an anti-counterfeiting label is its instability in and sensitivity to harsh environments. Often, low temperatures are used to preserve DNA and prevent it from getting degraded due to oxidation, hydrolysis and alkylation over time (Wetmur and Davidson, 1968). Apart from high temperatures, exposure to UV light and unfavorable pH conditions can significantly affect the chemical structure of DNA resulting in its degradation. Association of DNA based anti-counterfeiting labels with products must therefore be accompanied with logistics that favor its protection which can result in increased costs. An inexpensive route to protect DNA in labels without use of excessive supplemental resources is therefore desirable. Coating of DNA with an external protective layer before it is made a part of the label may offer a possible solution.

Various methods have been proposed in the literature for the protection of DNA in harmful environments. One of these methods is coating the DNA with silica (Liu et al., 2017; Paunescu et al., 2013; He, 2003). While successful encapsulation of DNA in silica nanoparticles has been demonstrated on multiple occasions, its extraction is of primary concern (Numata et al., 2004; Fujiwara et al., 2007). Paunescu et al., for example, successfully extracted DNA from silica substrates using a novel approach (Paunescu et al., 2013). They initially used polycondensation of tetraethoxysilane to synthesize a silica substrate for DNA immobilization following coating with another layer of nonporous silica for encapsulation. Extraction of DNA was achieved using hydrogen fluoride which can dissolve silica. Demonstrated stability of DNA encapsulates at 200°C indicated potential applications in barcoding of commercial goods and polymers. Elsewhere, DNA was immobilized on magnetic nanoparticles and then coated with a layer of silica allowing both DNA protection and easy separation (Puddu et al., 2014). While excellent results were achieved using these routes, hydrogen fluoride can prove to be toxic and corrosive, mandating employment of skilled personnel for DNA isolation (Stavert et al., 1991). Healthier alternatives to hydrogen

fluoride therefore need to be identified to extract DNA and confirm its sequence. It may however be concluded that the idea of protecting the DNA with nanoparticles can prove to be a useful approach.

Nanohybrids are another class of materials defined as hetero-nanoparticles that have organic/inorganic components with discreet domains (Zhao, 2019) and have been used to successfully encapsulate DNA. Choy et al., for example, used magnesium nitrate based layered double hydroxide (LDH) inorganic complex to form stable DNA-LDH nanohybrids (Figure 2) (Choy et al., 2004). Synthesized nanohybrids demonstrated exceptional stability at temperatures as high as 300°C and chemical resistance at pH greater than 4. Successful extraction of DNA was achieved using 0.01M HCl. Park et al., alternatively used metal hydroxide nanosheets to encapsulate DNA in spherical nano shells (Park et al., 2010). An easy recovery of DNA was demonstrated at low pH by placing the DNA core nano shells in Ethylenediaminetetraacetic acid (EDTA) for 1 hr. While nanohybrids offer excellent protection against high temperatures and harsh chemicals, their contribution towards protecting DNA under UV light needs to be further explored. Moreover, synthesis of such nanoparticles may not be cost effective.

While significant progress is being made using nanohybrids and silica for DNA stability and protection, other nanomaterials need to be explored for their desirable traits. Han and coworkers demonstrated that a DNA/Gold nanoparticle conjugate is more stable under the influence of biological and chemical substances, in comparison to bare DNA (Han et al., 2006). The increased thermal stability of DNA when conjugated with nanoparticles has also been established in the literature (Li et al., 2013). Nanoparticles can therefore make an excellent contribution towards the stability and protection of DNA under stressful conditions. The stability of DNA in these complexes strongly indicates that nanoparticles support the preservation of the DNA molecule against harmful environments. With the application of DNA as an anti-counterfeiting tag, the environmental effect on the DNA as the tag moves along the supply chain needs to be minimized.

On a commercial front, remarkable breakthroughs have been achieved by Applied DNA Sciences, Inc. Their botanical DNA authentication markers were found to be resistant to UV light and X rays. Further, the markers were found to be stable at temperatures as high as 250°C and at extreme pH ranges (Hayward and Meraglia, 2011). While the stability of DNA markers claimed is indeed noteworthy, information on how the markers are protected is not readily available.

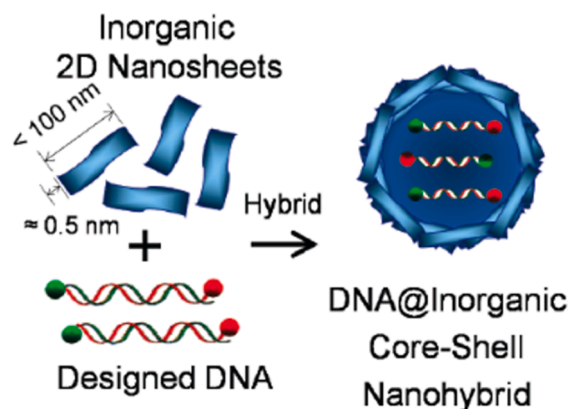


Fig. 2. Protection of DNA using Inorganic Nanohybrids (Park et al., 2010) (Printed with permission from American Chemical Society).

3.2.2. Association of DNA tags with products and integration with current technologies

Advantages of the use of DNA labels for anti-counterfeiting applications come along with the challenge of its association with individual products and integration with current technologies. Its strategic placement is important to prevent exploitation and security breach by counterfeiters. Further, a solution that calls for a minimal change in current state of logistics such as integration with bar codes, QR codes and RFID is also highly desirable.

Various procedures have been proposed for placement of DNA based authentication sequences onto products. Mead and coworkers for instance discussed how currency stained with botanical DNA was successfully tracked following their misappropriation. DNA was incorporated in the ink of degradation unit, which upon being broken stained the currency with ink containing DNA (Mead et al., 2014). While this technique is specific to cash and valuables transportation systems, a more general approach allowing tracking and authentication of consumer goods in the supply chain is needed. Hashiyada successfully developed a printable biometric ink which can be used for product authentication employing a rather simple approach (Hashiyada, 2004). Double stranded DNA was initially mixed with Infrared light sensitive pigment followed by combining it with additives and solvents resulting in an invisible ink. Liu et al., alternatively used SYBR green to successfully synthesize a DNA based invisible ink which fluoresces under the influence of UV light (Figure 3(b)) (Liu et al., 2017). They initially used

gelatin nanoparticles to encapsulate SYBR labelled DNA and ensure retention of fluorescence following which it was coated with silica for protection. While notable resistance of the DNA labels was achieved at temperatures as high as 120°C and stability of at least 12 months, the procedure involved multiple steps. Although the idea of including DNA labels that can be printed seems effective with minimal change in current state of technology, containers with products may be replaced by counterfeiters. Product arbitrage further emphasizes drawbacks of such authentication labels containing DNA, calling for alternatives.

Arbitrage is defined as the exploitation of dissimilarities in regulations and laws across various nations and the practice is often used to maximize illegitimate profits (Gloukhovtsev et al., 2018). Difference in price of important products in various parts of the world can possibly be exploited for their counterfeiting, allowing replacement of authentic products from their containers (Motohashi and Venturing, 1997). Placement of anti-counterfeiting labels directly onto products may prove to be a better approach.

Significant breakthroughs have been made by Paunescu and coworkers for effective association of products with DNA based authentication sequences. As discussed earlier, they attempted direct inclusion of silica coated DNA in polymer products made of poly-sulfone and poly-vinylchloride (PVC) blends (Figure 3 (a)) (Paunescu et al., 2013). Similarly, Altamimi and coworkers proposed direct incorporation of short DNA sequences in lactose containing tablets as a part of excipient (Altamimi et al., 2019). Although shelf life of incorporated DNA was



Fig. 3. (a) Polymers containing DNA sequences (Paunescu et al., 2013) and (b) invisible ink containing DNA for product authentication (Liu et al., 2017) (Printed with permission from Wiley and Royal Society of Chemistry).

determined to be a function of time, it was successfully detected even after 6 months of storage. Elsewhere, DNA sequences were attached to magnetic nanoparticles and included in liquid consumer goods such as milk and oil (Puddu et al., 2014; Bloch et al., 2014). This allowed easy retrieval of the sequences from which DNA could be extracted later for analysis. Except for a tedious DNA extraction process, this approach appears highly beneficial as individual products can be labelled and authenticated. Further, a cost of approximately 0.2 US \$ per ton of liquid product was proposed demonstrating economic feasibility of this method.

Jung and coworkers proposed a rather simple but effective approach for labelling of pharmaceutical products. DNA sequences <200 base pairs in length were made a part of pharmaceutical grade printing ink and were sprayed directly onto products (Jung et al., 2019). The DNA was found to be stable for at least 2 years and its presence was confirmed using PCR based detection. However, no mechanism to protect the DNA was employed. While drug capsules were employed in this study, their approach may be applied to other important consumer goods.

While much academic research has not been done on applicability of DNA based product authentication in supply chains, significant progress has been made by commercial entities. SelectaDNA® for example, has proposed practical solutions for labelling products with DNA markers including aerosols that can be sprayed onto products. DNA markers have also been integrated with products at a manufacturing level and attempts to extract DNA can result in its damage, protecting product authenticity (Hayward and Meraglia, 2011). These markers were found to be stable under harsh environmental conditions. While multiple attempts have been made to solve DNA stability issues on a commercial front, not a lot of information is available on their underlying technology.

Indeed, stability and strategic association of DNA with consumer products is important for the success of this technology. As stated, these issues to an extent have been solved by commercial organizations. Detection of DNA, however, remains a major concern since it can be a time-consuming and expensive process. The section that follows discusses detection strategies of DNA in further detail.

3.2.3. Detection of DNA

The application of a DNA based anti-counterfeiting system may be fully realized with easy and cost-effective detection of the unique DNA sequence tags. Various routes are available and newer ones are being proposed as we move towards the practical application of this technology. Traditionally, methods relying on Polymerase Chain Reaction (PCR) have been used to confirm the presence of correct DNA sequence. Although well established, these methods are invasive and involve sample destruction for verification. Further, PCR based methods can be a time-consuming process requiring several hours and equipped laboratories. Rapid, inexpensive, and field applicable methods are therefore highly desirable.

3.2.3.1. PCR based methods and Sequencing. Amplification based methods such as PCR, RT-PCR and sequencing are conventional routes used to confirm the presence of specific DNA sequence. Sanger sequencing is an established technique that has been applied in anti-counterfeiting (Puddu et al., 2014). However, extraction and purification processes may result in loss of DNA. Liu et al., addressed this issue by amplifying the extracted DNA and then proceeded with sequencing of the sample (Liu et al., 2017). Alternatively, Hashiyada sub-cloned DNA fragments into a plasmid, grew them in bacteria and finally isolated and sequenced the DNA (Hashiyada, 2004). Since sequencing technology determines the exact sequence of the arrangement of DNA bases, its accuracy may be considered unmatched with any other technique. Moreover, such techniques can detect DNA in extremely low concentrations. Sequencing therefore may be considered the gold standard for the detection of DNA authentication tags.

Quantitative PCR is another technique that has gained popularity for detection of DNA based anti-counterfeiting tags (Bloch et al., 2014). Other techniques such as sequence specific isothermal DNA amplification which can provide a simple positive or negative readout have also been used (Jung et al., 2019).

Polymerase Chain Reaction based approaches can offer numerous advantages and have been used extensively in product authentication. However, it is important to note the time required to prepare the samples is a major drawback. Further, these methods are expensive, invasive and require a laboratory skillset, presenting an obstacle in their field-based applications.

3.2.3.2. Surface Plasmon Resonance. Following the demonstration of biosensing by surface plasmon resonance (SPR) by Liedberg and Nylander in 1982, this technique has been used in many applications by the scientific community (Liedberg et al., 1983). SPR makes use of diffraction due to the excitation of the surface plasmon waves (Otto, 1968; Kretschmann and Raether, 1968) and can be utilized for detection of DNA anti-counterfeiting tags.

The use of SPR for the detection of pathogens has been well established in the literature (Homola, Oct. 2003)–(Huang et al., 2011). The technique can also be used for the detection of unique DNA sequences wherein single stranded complimentary sequences are immobilized on surface and change in plasmon resonance is observed upon hybridization. Different versions of DNA hybridization based SPR can also be found in the literature. He et al., for example used gold based SPR for ultrasensitive (<10 Pico Molar) detection of DNA (He, 2000). Endo et al., alternatively used a variant, Localized Surface Plasmon Resonance (LSPR) to detect even lower amounts of DNA, with a detection limit of 0.67 pM (Endo et al., 2005).

While the technique seems apt for detection of DNA in anti-counterfeiting tags, equipment complexity and cost ineffectiveness are major hindrances for its application. Moreover, this technique can only give a positive or negative readout and may not be useful in determining the exact sequence of DNA used.

3.2.3.3. Electrochemical detection. Electrochemical methods are gaining popularity in biosensing applications for the detection of pathogens and microorganisms in general. Electrochemical biosensors typically make use of single stranded DNA immobilized on an electrode with a sequence complementary to the DNA of interest (Drummond et al., 2003). The difference between the electrical properties of single stranded DNA and hybridized double stranded DNA help in identifying the correct DNA sequence, making it suitable for anti-counterfeiting applications. Cyclic voltammetry performed using a Potentiostat is often used as a method to study such changes in electrochemical properties of the sample.

Graphene and graphene oxide have recently gained attention due to their excellent electrical properties. These materials have also been employed for the detection of specific DNA sequences using electrochemical methods. The structural defects in graphene oxide are considered to be beneficial for electrochemical applications (Banks et al., 2005; McCreery, 2008). Tiwari et al., combined the excellent properties of graphene oxide with chitosan to detect *E. coli* DNA, using Electrochemical Impedance Spectroscopy (Tiwari et al., 2015). Gong et al., combined graphene with Nafion to synthesize a stable film which could detect the presence of a specific HIV gene at concentrations as low as 2×10^{-14} M (Gong et al., 2017).

Among other nanomaterials, conjugated oligonucleotides and gold nanoparticles were used, with the changes in binding conductivities as a method to detect target DNA (Drummond et al., 2003). The combination of various nanoparticles to detect DNA has also been observed in the literature. Chen et al., (Chen et al., 2016) for example combined graphene with gold nanoparticles to detect specific DNA sequences. While most examples stated have used electrochemical biosensors to detect pathogens or diseases, the technique has not yet been applied in DNA

based anti-counterfeiting systems.

Although major advantages of this technology over PCR and SPR based approaches include availability of portable electrochemical sensor systems (Nordin et al., 2017) and cost effectiveness (Rowe, 2011), reduction of multiple sample preparation steps is preferable for field applicability. Further, as with SPR, a mere positive or negative response is expected, and complete DNA sequence cannot be determined using this approach.

3.2.3.4. Colorimetric Biosensor. For a widely applicable system that can detect DNA from authentication tags, its ease of use, inexpensiveness and rapidity is crucial. Moreover, a biosensor that can achieve sensitive detection in a low resource setting is highly desirable.

Park and coworkers proposed a DNA chip-based biosensor where strand hybridization results in a positive readout confirming product authenticity (Park et al., 2010). Although established, this approach may not be commercially viable as various products would be associated with unique DNA sequences. An extensive inventory of such chips will therefore have to be maintained adding a layer of complexity. Remarkable electrical properties of nanomaterials and their application in biosensing have been discussed in earlier sections. Gold based nanoparticles have demonstrated exceptional surface and optical properties which can be used for detecting DNA from authentication tags.

While evidence is scarce where gold nanoparticles have been used to detect DNA in anti-counterfeiting systems, numerous examples exist where they have been used to detect DNA extracted from pathogens. Xia and coworkers for instance succeeded in detecting DNA at picomolar concentrations using target DNA specific probes, gold nanoparticles and conjugated polyelectrolyte. Stability of gold nanoparticles, which is indicated by maintenance of red appearance, was seen in the presence of target DNA. Absence of target DNA led to their aggregation indicated by their blue appearance (Xia, 2010). Baetsen-Young et al., followed a similar approach with fewer reagents where target DNA and specific probes were allowed to hybridize following addition of gold nanoparticles. Upon addition of sodium chloride, stability of gold nanoparticles indicated presence of target DNA and their aggregation indicated its absence, achieving a remarkable detection limit of 2.94 fM (Baetsen-Young et al., 2017). They used dextrin capped gold nanoparticles which, initially proposed by Anderson et al., demonstrated enhanced stability under the influence of alkaline environments (Anderson et al., 2011). DNA biosensors which use surface properties of nanoparticles such as gold can allow for simple and rapid detection of DNA from anti-counterfeiting labels. A primary advantage of such methods is their application without the use of complicated, expensive equipment and results readily visible to the naked eye.

The biosensor technologies discussed can provide a true/false output and not the sequence in which nucleotides are arranged which is achievable only with a PCR based approach. It is also noteworthy that all the stated technologies are invasive in nature and will require destruction of label for analysis.

4. Conclusion

In times of pandemic such as our current situation, fraudulent medical care products, diagnostics, and treatment cannot be allowed to penetrate the supply chain and destroy the fragile health of the sick and vulnerable populations. DNA can provide for an excellent anti-counterfeiting tag due to its relative ease of synthesis, encryption of sequences and ability to store an immense amount of data. Duplication of DNA based authentication tags for counterfeiting, although possible, can prove to be difficult as correct pair of primers and sophisticated laboratory equipment is required.

A critical issue that needs attention is the attachment of DNA taggants with products. Combination of DNA taggants with traditional authentication labels may not be very effective as labels on packages or

containers may be easily replaced. An ideal solution therefore is to have DNA incorporated directly onto the products which can also address the issue of arbitrage. Since transportation of products can take longer durations, protection of DNA in harsh environments is important. Further, rapid, inexpensive, and non-destructive determination of the DNA sequence is a major challenge and additional research in this area is necessary.

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CRedit authorship contribution statement

Saad Asadullah Sharief: Conceptualization, Methodology, Visualization, Data curation, Writing - Original draft preparation, Writing - Reviewing and Editing, Investigation. **Prem Chahal:** Supervision. **Evangelyn Alocilja:** Conceptualization, Methodology, Writing - Reviewing and Editing, Supervision.

Declaration of Competing Interest

The authors declare that they 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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