frontiers | Frontiers in Physics

REVIEW
published: 12 May 2022
doi: 10.3389/fphy.2022.869537

Applications of Terahertz Spectroscopy in the Detection and Recognition of Substances

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Recently, terahertz spectroscopy has received a lot of attention because of its unique properties such as biosafety, fingerprint spectrum, and good penetration. In this review, we focus on the research progress of terahertz spectroscopic techniques for the detection and recognition of substances. First, we describe the fundamentals of terahertz spectroscopy. Then, we outline the applications of terahertz spectroscopy in biomedicine, agriculture, food production, and security inspection. Subsequently, metamaterials, which have recently received extensive attention, are also investigated for the applications in terahertz spectroscopic detection and recognition of substances is illustrated. Finally, the development trend of terahertz spectroscopy for substance detection and recognition is also prospected.

Keywords: terahertz spectroscopy, substance detection, biological application, agriculture application, safety inspection, metamaterial

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Specialty section:
This article was submitted to Optics and Photonics, a section of the journal Frontiers in Physics

Received: *04 February 2022*
Accepted: *22 April 2022*
Published: *12 May 2022*

Citation:
Fu X, Liu Y, Chen Q, Fu Y and Cui TJ (2022) Applications of Terahertz Spectroscopy in the Detection and Recognition of Substances. Front. Phys. 10:869537. doi: 10.3389/fphy.2022.869537

INTRODUCTION

The Terahertz (THz) band of the electromagnetic spectrum lies between microwave and far infrared, and is usually defined as electromagnetic radiation from 0.1 to 10 THz, corresponding to a wavelength range of 3 mm to 30 μm [1]. THz radiation possesses the following remarkable characteristics. 1) Fingerprint spectrum. The photon energy of a THz radiation is similar to the excitation energy of the rotational transitions in molecules, so information such as molecular vibration and rotation is contained in the terahertz spectroscopy. This is the fingerprint characteristic of terahertz spectroscopy, and it is also an important reason why it can be applied to substance detection and recognition. 2) Good Bio-safety. Compared to X-rays, THz waves have a very low photon energy of about 4 meV at 1 THz and are non-ionizing [2]. Therefore, THz waves do not cause ionization damage to samples such as biological tissues [3, 4]. 3) Coherent measurement. THz waves are usually generated by coherent laser pulses using nonlinear optical effects or dipole oscillations driven by coherent currents, so THz waves are coherent and can directly measure the amplitude and phase information of the electric field [2]. 4) High spatial and time resolution. Compared with microwaves and millimeter waves, THz waves have shorter wavelengths and can achieve higher resolution [5, 6]. THz pulses have good time resolution with pulse width on the sub-picosecond to picosecond time scale, which allows the analysis of transient changes in molecules, electrons, etc. [7, 8]. Thus, it is possible to use THz time-resolved spectroscopy in the detection and recognition of substances. 5) Good penetration. THz waves have good penetration and can penetrate general dielectric materials including plastics, clothing, and ceramics [9, 10]. This gives terahertz spectroscopy the potential to detect dangerous goods [11, 12]. Although THz waves are easily absorbed and lost by polar molecules such as water [13], the absorption spectroscopy at this time can also be used to evaluate the water content of the sample [14, 15].

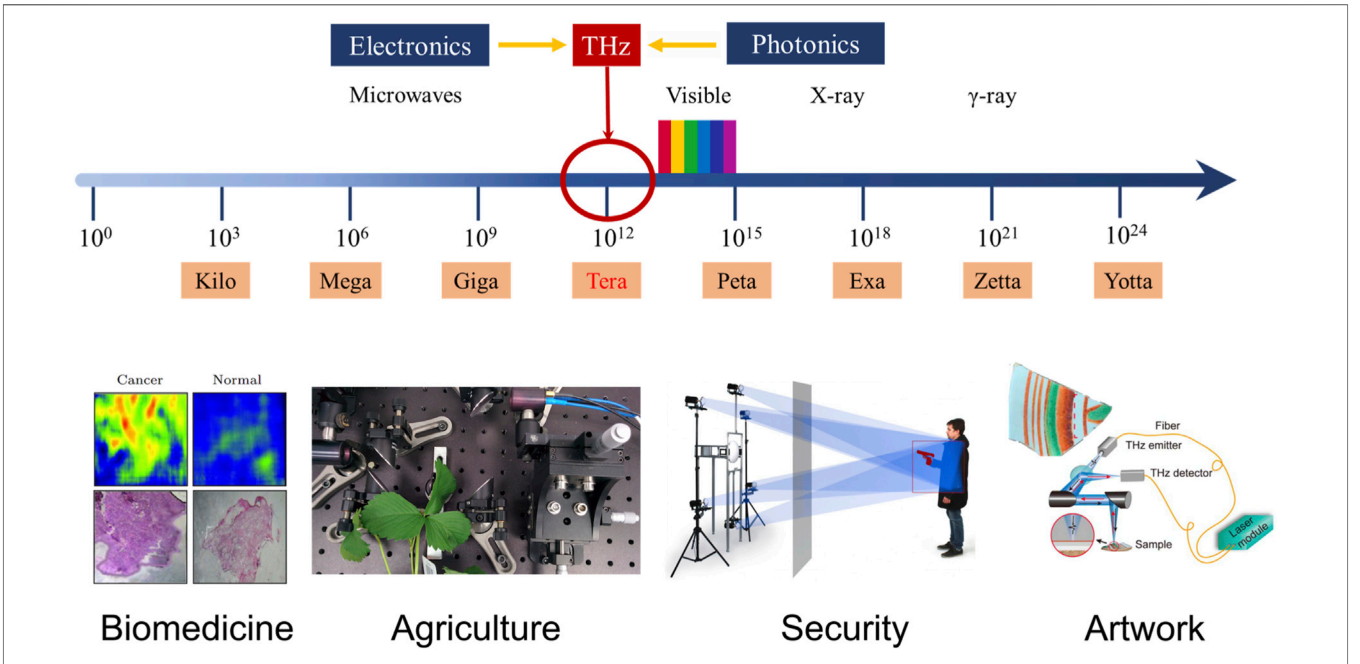

FIGURE 1 | Terahertz spectroscopy and some typical applications [1, 22, 25, 29, 30]. Reproduced with permissions. © 2013 Chinese Physical Society and IOP Publishing Ltd. © 2017 IEEE. © 2020 Springer Science Business Media, LLC, part of Springer Nature. © 2021 The Japan Society of Applied Physics.

THz radiation has so many properties that it has great potential for applications in biomedicine [3, 16–19], agriculture and food manufacturing [20–23], security inspection [24, 25], and many other fields [26–29], as shown in **Figure 1**. However, due to the limitation of THz wave generation and detection technologies, THz wave has not received much attention and research before 1990s, which is called "THz Gap" [2]. With the development of ultrafast optoelectronics and low-scale semiconductor technology, terahertz spectroscopy has made rapid progress, and related research and applications have focused more and more attention.

As aforementioned, we can conclude that terahertz spectroscopy can provide a comprehensive response to the optical characteristics of a sample in the detection and recognition of a substance. The current terahertz spectroscopic technologies can generally be divided into three types: THz Time-Domain Spectroscopy (THz-TDS) [2], time-resolved terahertz spectroscopy [31, 32] and THz emission spectroscopy based on the concept of laser THz emission microscopy [33]. The most commonly used technique is THz-TDS, which was first proposed in the 1980s [34, 35]. It mainly uses a broadband pulsed radiation source generated by the excitation of semiconductor materials using ultrashort laser pulses [36]. Based on the coherent measurement method, THz-TDS provides the variation of the THz electric amplitude with time after a THz pulse interacts with the sample. The frequency-domain amplitude and phase information of the THz response of the sample can also be calculated by performing a Fourier transform on the measured time domain results. Hence, electromagnetic parameters such as absorption coefficient, refractive index and dielectric constant of the sample can be easily extracted. Terahertz spectroscopy also has the advantages of wide bandwidth, large dynamic range, transient feature, and high sensitivity. Currently, the THz-TDS systems can achieve excellent test performances: a broad bandwidth of about 0.1–3 THz (some can even extend to 10 THz), a high peak signal-to-noise ratio greater than 100 dB, and a frequency resolution up to 10 GHz. Besides, the sampling time can be as low as a few seconds [37, 38].

Taking into account different samples, different detection standards, etc., the measurement modes of THz-TDS systems can usually be divided into transmission type, reflection type, attenuated total reflection type, etc. At present, the common THz-TDS experimental systems are mainly transmission type and reflection type. A typical THz-TDS experimental setup is shown in **Figure 2** [1]. An ultrafast pulse is generated by a femtosecond laser, and then divided into pump beam and probe beam after passing through a beam splitter. The pump beam excites a THz emitter (e.g., a photoconductive antenna) to generate a THz time-domain pulse, which is collimated and focused on the sample by a parabolic mirror. Then, the THz pulse carrying the sample information is collimated and refocused onto the THz detector (e.g., electro-optical crystal). The probe beam collinear with the THz beam is used to gate the detector and measure the instantaneous THz electric field. A delay stage is used to adjust the time delay between the pump beam and probe beam and allows the THz temporal profile to be iteratively sampled. The time domain waveform of the THz pulse is obtained by scanning the time delay. Afterwards, the time domain waveform is amplified by a lock-in amplifier and processed by a computer. In most cases, reflection and transmission measurement modes differ only in that the former receives reflected pulses, while the latter receives transmitted pulses. Transmission spectroscopy is limited by the maximum dynamic range, especially when the sample absorbs THz radiation strongly, resulting in a lower penetration depth. In contrast, the reflection spectroscopy is determined by the signal

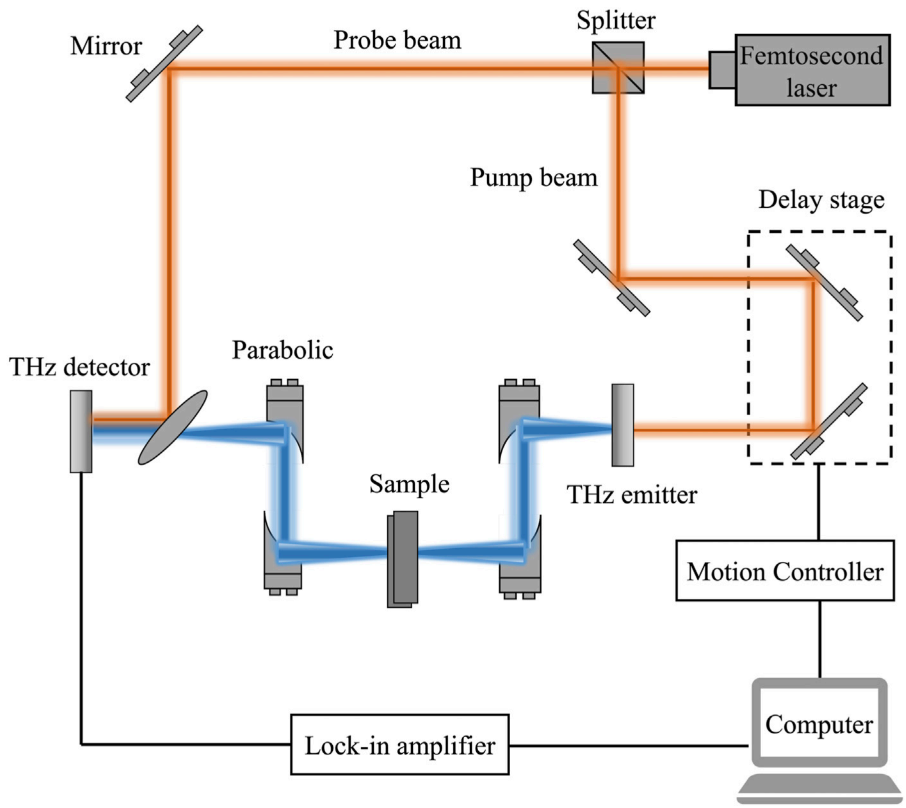

FIGURE 2 | Schematic of a typical transmission-type THz-TDS experimental setup [1].

phase and amplitude accuracy rather than the sample, the maximum absorption depends on the signal-to-noise ratio (SNR). Thus, reflection-type THz-TDS will be more applicable to absorbing materials or devices [39]. In addition, in most experiments, the experimental setup will be placed in a dry air or nitrogen purged box in order to avoid the absorption of THz waves by moisture in the air.

Our paper focuses on a review of the application of terahertz spectroscopy for the detection and recognition of substances, describes the fundamentals of terahertz spectroscopy, and provides an overview of the applications of terahertz spectroscopy in biomedicine, agriculture and food production, and security inspection. Subsequently, the applications of metamaterials in terahertz spectroscopic detection and recognition of substances are discussed. In addition, the development trend of terahertz spectroscopy applied to substances detection and recognition is also prospected.

APPLICATIONS OF TERAHERTZ SPECTROSCOPY

Terahertz Spectroscopy for Biomedical Applications

As mentioned in the previous section, THz waves have fingerprint spectrum, so the terahertz spectroscopy of various biomolecules is characteristic and can be relied upon for the identification of various biomolecules. Additionally, the non-ionizing nature of THz radiation makes it possible to detect biological tissues non-invasively. THz waves are strongly absorbed by polar molecules such as water, while biomolecules have limited absorption, so the THz spectrum can be used to distinguish the water content of biological tissues to assess their status. This, coupled with the penetrating of THz and its relatively high resolution, suggests that terahertz spectroscopy has promising applications in the biomedical field [3].

As early as 2002, Ferguson B et al. used THz-TDS to record terahertz spectroscopy of the four nucleobases [adenine (A), cytosine (C), guanine (G) and thymine (T)] and the corresponding nucleosides that form the deoxyribonucleic acid (DNA) building blocks, as shown in **Figure 3A,B** [40]. As can be seen, the spectrum of each molecule consists of a series of resonances distributed between 1 and 3.5 THz. An absorption peak is observed at each resonance, and the characteristic change is related to the refractive index. In addition, due to the reduction of the bond length in the system at low temperatures, the position of the bands usually shifts towards high frequencies when cooling. Globus T et al. measured the spectroscopy of DNA samples in liquid phase and could distinguish the spectral patterns for native and denatured DNA [41]. Zhang W et al. measured the THz absorption fingerprints of DNA in microliter DNA solution [17], as shown in **Figure 3C,D**. Then, they clarified that the fingerprint characteristic comes from DNA locally cross-linked by hydrogen

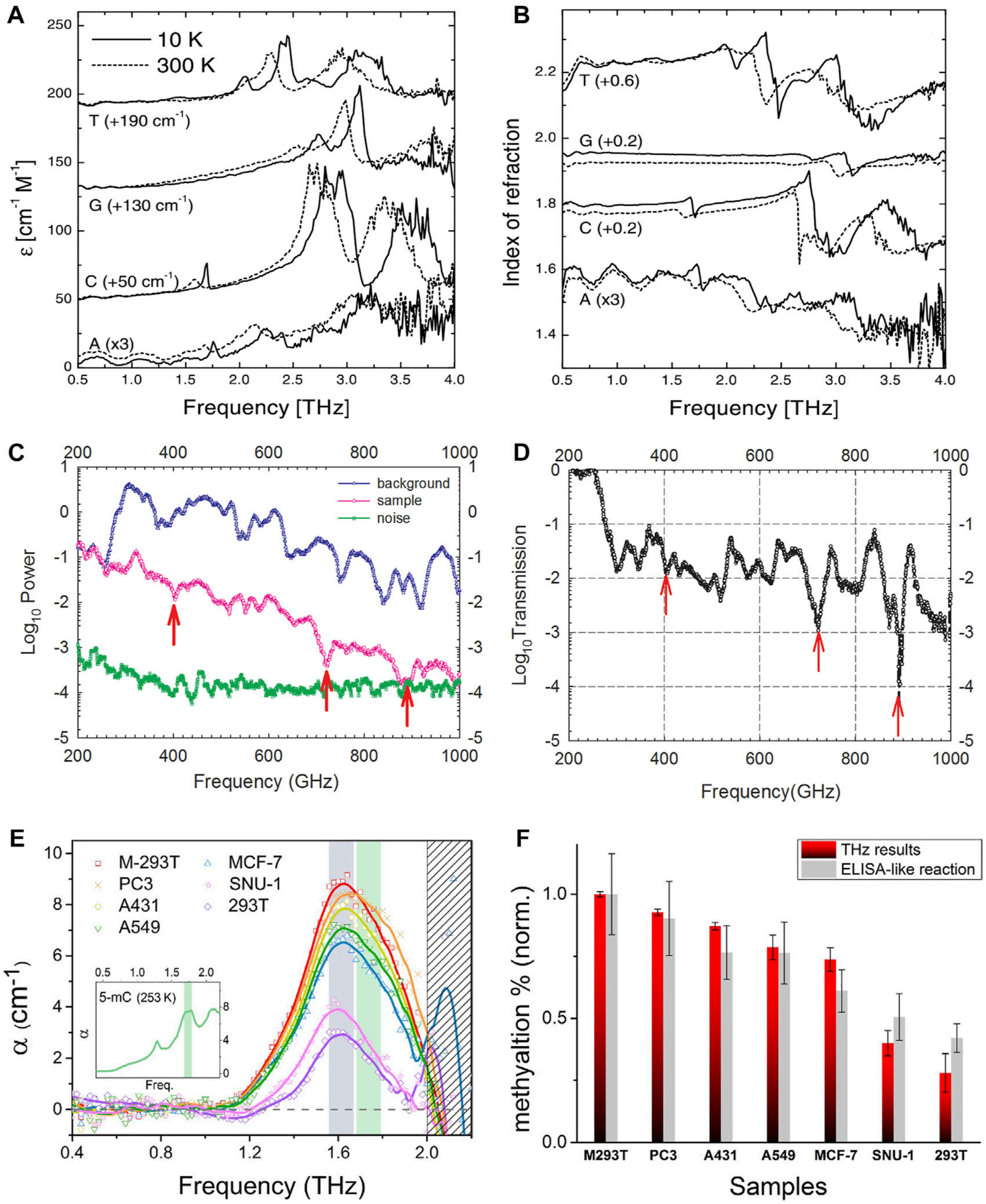

FIGURE 3 | (A) Absorption coefficients and **(B)** refraction indices of the nucleobases A, C, G and T at 10 and 300 K [40]. Reproduced with permission. © 2002 IOP Publishing Ltd. Spectra of microliters of DNA solution **(C)** background, sample and noise floor and **(D)** spectra after exclusion of background effects [17]. Reproduced with permission. © 2013 AIP Publishing. **(E)** THz resonance peaks for DNA samples after baseline correction, genomic DNA from different cancer types (PC3, A431, A549, MCF-7, and SNU-1 cell lines) has the same resonance peak at 1.67 THz [50] **(F)** The degree of DNA methylation for each DNA sample. The magnitude of the resonance peak for each sample was quantified by the amount of genomic DNA methylation and compared with commercial DNA methylation quantification measurements (enzyme-linked immunosorbent assay like reaction method (ELISA)-like reaction method, Epigentek Group, Inc.) [50]. Reproduced under a Creative Commons Attribution 4.0 International License. © 2016 Springer Nature.

bond. In 2013, Tsurkan MV et al. studied the THz spectra of herring degradation DNA using a femtosecond laser and 2 THz spectroscopy methods based on Backward-Wave Oscillator (BWO) and a high Q cavity frequency synthesizer, and showed that herring DNA has characteristic absorption peaks at 306 GHz, 339 GHz, and 375 GHz, providing a method for more accurate analysis of DNA THz spectra [42]. In 2015, Tang M et al. applied terahertz spectroscopy to the detection of DNA mutations, and their method successfully performed label-free analysis of single-base mutations in DNA molecules [43]. Besides, terahertz spectroscopy can be used to detect amino acids [44–46], proteins [47–49], and other biomolecules with good results.

Carcinogenesis causes chemical and structural abnormalities in biomolecules, one of which is widely known to be abnormal methylation of DNA. In 2016, Cheon H et al. proposed that molecular resonances could be monitored using THz-TDS in aqueous solutions of genomic DNA from cancer cell lines [50]. The quantification of resonance signals led to the identification of cancer cell types with some degree of DNA methylation. It was shown that identical resonance peaks at 1.67 THz were found in genomic DNA from various cancer types (PC3, A431, A549, MCF-7, and SNU-1 cell lines), and the THz resonance peaks for DNA samples after baseline correction are shown in **Figure 3E**. The magnitude of the resonance peaks for each sample was quantified by the amount of genomic DNA methylation, the degree of DNA methylation for each DNA sample is shown in **Figure 3F**. This demonstrates that cancer cell DNA also has THz fingerprinting spectra and provides a way to diagnose cancer at the molecular level. Shortly after, Cheon H et al. applied this method to the detection of blood cancers [51], using THz-TDS to observe characteristic resonances of DNA in blood cancers at a frequency of about 1.7 THz, and used this to analyze their methylation levels. Subsequently, they applied THz radiation to the treatment of cancer [52].

Terahertz spectroscopy has been applied to human tissue scanning and cancer diagnosis since around 2000. Woodward RM et al. used the absorption characteristics of THz waves for polar molecules such as water [16], and they distinguished between carcinoma diseased tissue and normal tissue of human basal cell by terahertz spectroscopy. Compared to normal tissue, basal cell carcinoma shows positive THz contrast, while inflammatory and scar tissue shows negative THz contrast, whereby THz images can be further drawn, which can help to better diagnose diseases such as cancer. In 2006, Wallace V further studied this and explained how parameters related to reflected THz pulses provide information about the lateral spread of tumors [53]. In 2009, Ashworth PC et al. used terahertz spectroscopy for the identification of human breast cancer tissue and found cancerous samples with high refractive indices and absorption coefficients in the 0.15–2.0 THz range [54]. In 2014, Hou D et al. used terahertz spectroscopy to differentiate between normal and cancerous gastric tissues, with significantly different shapes and amplitudes between the absorption spectra of the two, and a clustering approach was used to achieve automatic identification of gastric cancer [55].

In 2014, Meng K et al. found that paraffin-embedded gliomas had higher refractive index, absorption coefficient and dielectric constant than normal brain tissue under the terahertz spectroscopy [56]. In 2019, Gavdush AA et al. observed differences in THz spectra of intact tissue and gliomas of grades I to IV, reflecting the potential of terahertz spectroscopy in the intraoperative label-free diagnosis of human brain gliomas. The experimental setup is shown in **Figure 4A** [57]. In 2021, they further proposed physical models describing the THz permittivity of healthy and pathological brain tissue, on the basis of the Double Debye (DD) and Double Overdamped (DO) oscillator models [19]. The DO model and summation rule were applied *ex vivo* to estimate water content in intact tissues and gliomas, and the observed results are in good agreement with previously reported data demonstrating that water is a major endogenous label for brain tumors in the THz range. Besides, terahertz spectroscopy is also used in the examination of human colon tissue [58, 59], oral tissue [60], pigmented skin nevi [61], liver tissue [62] and related cancers.

Considering the differences between cancer patients, THz imaging technologies were employed to aid the diagnosis of cancer. For example, Bowman TC et al. in 2015 used THz pulse imaging to image and analyze heterogeneous breast cancer tissue [63]. They proposed a THz imaging method capable of distinguishing heterogeneous regions of breast tumors, and the results were compared and validated with standard histopathology images. In addition, THz imaging has also been applied to the diagnosis of colon cancer [64, 65], gastric cancer [66], skin cancer [67], liver cancer [30], etc. With the popularity of artificial intelligence in recent years, artificial intelligence techniques such as machine learning have also been used to diagnose cancer by combining with terahertz spectroscopy and imaging techniques [68–70]. Recently, Liu W et al. devised an automatic recognition strategy for THz pulse signals in breast invasive ductal carcinoma (IDC) based on wavelet entropy feature extraction and machine learning classifier [69]. Using principal component analysis method and machine learning classifier to automatically classify THz signals from breast IDC samples, the accuracy, sensitivity, and specificity of breast IDC recognition can reach 92.85%, 89.66%, and 96.67%, respectively.

In addition to diagnosing cancer, terahertz spectroscopy can also be used for the diagnosis of diseases such as diabetes. As early as the beginning of this century, researchers have used terahertz spectroscopy in dental care [71–74], for example in the detection of dental caries, where there is a higher attenuation of THz radiation in decayed enamel than that in healthy enamel. In 2010, Sy S et al. investigated in detail the correlation between THz properties of liver tissue, water content, structural changes, and cirrhosis, showing significant differences between the THz properties of normal and cirrhotic tissues [75]. Recently, Lykina AA et al. used terahertz spectroscopy to study plasma samples from diabetic and non-diabetic patients hoping to complete the assay nondestructively [76, 77]. The results showed that the normalized refractive index of particles from diabetic samples in the range of 0.2–1.4 THz increased by an average of 9–12% compared to particles from non-diabetic samples, and their terahertz spectroscopy were also spatially separated in principal component space. Detection of corneal edema can prevent corneal disease from reaching its end stage, and Ke L et al. assessed the degree of corneal edema by means of high-sensitivity THz broadband spectroscopy to detect corneal components at different depths. The process of THz signals acquired from the corneal surface and corneal subsurface is illustrated in **Figure 4B** [78].

Terahertz Spectroscopy for Agricultural Applications

Controlling the content of pesticide residues and harmful substances in food is an important measurement to ensure food safety. This is also an important application of terahertz spectroscopy in the agricultural field. As early as 2010, Hua Y

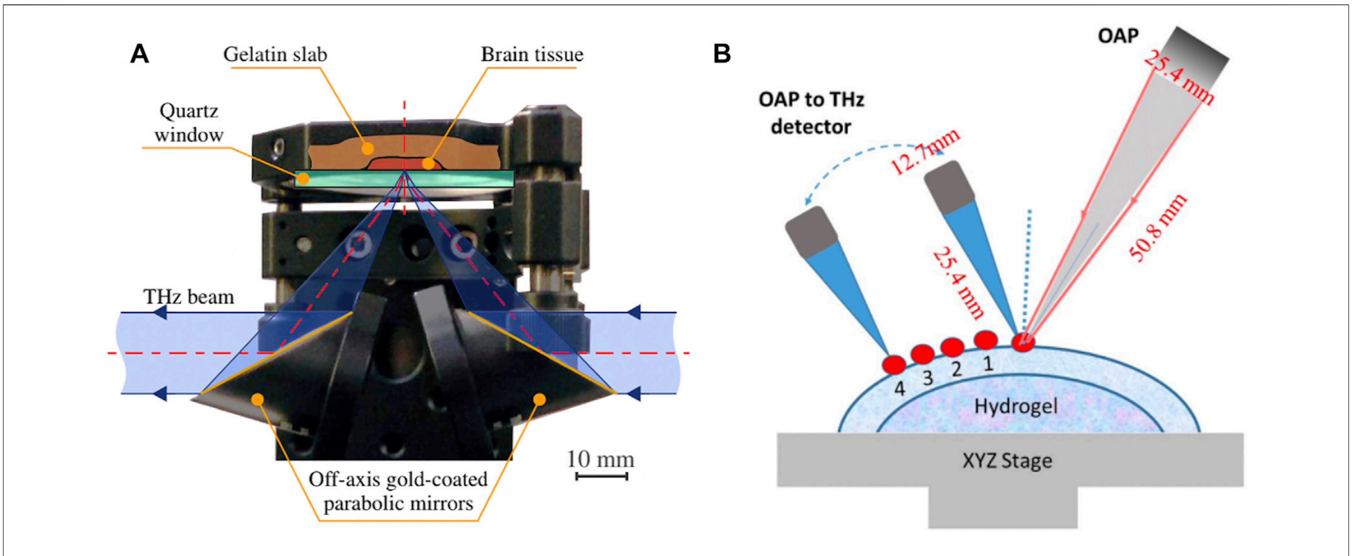

FIGURE 4 | (A) Reflection-mode terahertz spectroscopy unit for measuring gelatin-embedded human brain gliomas, based on an off-axis gold-coated parabolic mirror and a reference window on top of which tissue samples are placed [57]. Reproduced under a Creative Commons Attribution 4.0 Unported License. © 2019 SPIE. **(B)** The process of acquiring THz signals from the corneal surface and corneal subsurface [78]. Reproduced under a Creative Commons Attribution 4.0 Unported License. © 2021 SPIE. After acquiring the waveform once at an incident angle of 30°, a series of reflected beams were consecutively acquired at different distances (multiple points with a spacing of 2 mm) away from the direct reflection.

et al. carried out research on the application of terahertz spectroscopy to detect the pesticide residues [79]. They used THz-TDS at frequencies of 0.5–1.5 THz for cyfluthrin n-hexane solutions in the concentration range of 1–20 mg/ml, and proposed THz-TDS plus partial least squares (PLS) and nonlinear regression methods of simple least-squares support vector machine (LS-SVM) is an effective tool for the quantitative analysis of cyfluthrin n-hexane solutions. Then, Hua Y et al. investigated four pesticides and three food powders as well as polyethylene using THz-TDS in the frequency range of 0.5–1.6 THz [20], and used PLS regression for the detection and analysis of imidacloprid in polyethylene and glutinous rice powder at different weight ratios. The results of the study showed that the four pesticides could be distinguished from each other by their unique absorption peaks, as well as from food powders that did not have this feature. In addition, differences in refractive index between pesticides and food powders can be observed. Imidacloprid can be recognized by its absorption fingerprints in mixtures of imidacloprid and polyethylene and imidacloprid and glutinous rice flour, as shown in **Figure 5A,B**. Through the linear relationship between the weight ratio of imidacloprid and the absorption coefficient, the authors predicted the weight ratio of imidacloprid in the above two mixtures of powders and achieved a relative error of less than 5%.

Subsequently, more and more researchers applied terahertz spectroscopy to detect pesticides, insecticides, and fungicides residues. Wang Q et al. conducted a study on nitrofen [80], and then measured the THz spectrum of thiabendazole at room temperature [81]. Maeng I et al. used terahertz spectroscopy to detect seven different pesticide residues in wheat flour [82]. Baek SH et al. used THz-TDS to detect methomyl (a carbamate insecticide) in food, and the characteristic absorption peaks of methomyl measured at room temperature in the frequency range of 0.1–3 THz were 1, 1.64, and 1.89 THz as shown in **Figure 5C** [83]. The three absorption peaks of methomyl are linearly proportional to their concentrations in high-density polyethylene. The peak at 1 THz was used as the fingerprint for detecting methomyl in rice and wheat flours. **Figure 5D** shows the calibration curve for methomyl which showed a regression coefficient >0.957 and a detection limit <3.74%. Accuracy and precision expressed as recovery and relative standard deviation (RSD, %) in interday repeatability were in the ranges 78.0–96.5 and 2.83–4.98%, respectively. Although THz-TDS can be used to rapidly detect methomyl in food, its sensitivity still needs to be improved. Qin B et al. applied THz-TDS combined with fast search and find of density peaks (CFSFDP) clustering to detect carbendazim residues [21]. Zhang H et al. combined terahertz spectroscopy with an improved PLS method for the detection of the harmful additives Auramine O in the medicinal herb Pollen Typhae [84]. Liu W et al. applied machine learning to terahertz spectroscopy to detect aflatoxin B1 in soybean oil, and obtained an accuracy rate of over 90% [85]. Recently, Ma Q et al. combined terahertz spectroscopy with a back-propagation neural network (BPNN) for the quantitative analysis of ternary pesticide mixtures in wheat flour [23], and obtained good results with correlation coefficients of 0.9913, 0.9948, and 0.9923 for the prediction sets, the corresponding root mean square errors of 0.0211%, 0.0176%, and 0.0191%, respectively.

The application of terahertz spectroscopy in the agricultural field is far more than the detection of pesticide residues and harmful substances, but also in the identification of agricultural products [86–88], the detection of soil [89–91] and the detection

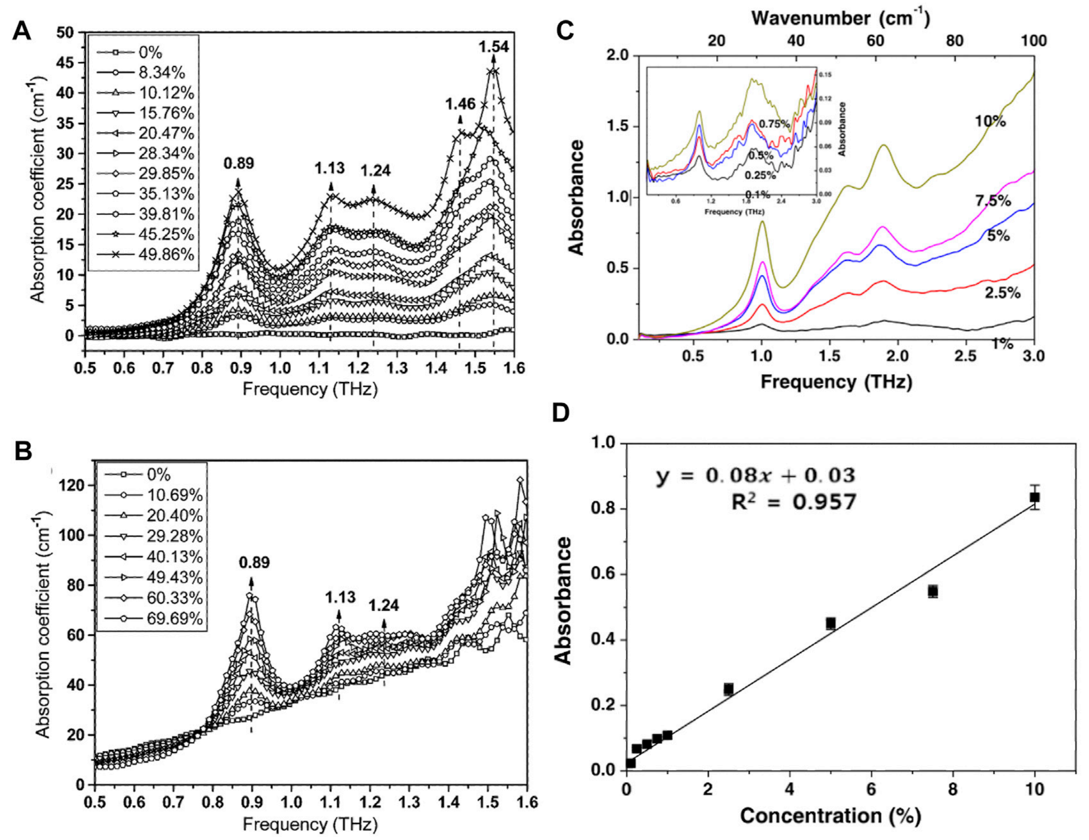

FIGURE 5 | THz absorption spectra of different weight ratios of imidacloprid **(A)** in polyethylene and **(B)** in glutinous rice flour. The labels show the corresponding weight percentages of imidacloprid in these mixtures. The numbers in the graph represent the location of the peaks and the arrows indicate an overall increasing trend in the weight ratio of imidacloprid in the mixtures [20]. Reproduced with permission. © 2010 IEEE. **(C)** Absorption spectra of methomyl at 0.1–3 THz and **(D)** calibration curve at 1 THz [83]. Reproduced with permission. © 2015 Springer Science Business Media New York.

of genetically modified crops [92–94]. More brand new applications are being explored.

Terahertz Spectroscopy for Safety Inspection Applications

In 2003, Campbell MB et al. proposed that terahertz spectroscopy could be used to non-destructively detect explosives and other weapons of mass destruction [95], and demonstrated that a THz spectral database that includes biological warfare agent (BWA) simulants, chemical warfare agent (CWA) simulants, explosives, pharmaceuticals, dozens of potential hoax materials as well as several types of papers and plastics used in common containers that may hold threat agents. Chen Y et al. in 2004 used Fourier transform infrared spectroscopy (FTIR) and THz-TDS to measure 14 commonly used explosive samples [96], and the far-infrared spectra of the explosives 2, 3-dinitro toluene (2,4-DNT), 4-nitro toluene (4NT), and 2, 6-dinitro toluene (2,6-DNT) measured via FTIR and THz were in good agreement with their structure and vibrational frequencies obtained using density functional theory (DFT) [97, 98]. In 2005, they applied THz diffuse reflectance spectroscopy (DRS) to the detection of explosives [24]. The experimental results show that DRS technology has higher sensitivity and easier sample preparation than transmission spectroscopy. In 2006, they obtained the absorption spectrum of the explosive hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) from the reflectance spectrum [99], and were able to distinguish RDX from other materials. In 2007, they used 0.1–2.8 THz THz-TDS to study the absorption spectrum of 17 explosives [100]. Most of the explosives show characteristic absorption, which can be used as a basis to build a relevant database. Moreover, they also considered that explosives are usually hidden, so they studied the absorption spectrum of explosives under the cover material to prove that the THz system can be used to detect hidden explosives. The experimental results show that the transmission spectra of RDX and tetramethylene tetranitramine (HMX) samples covered with three different materials - plastic, cotton, and leather at 0.1–3 THz agree well with those of the samples alone, which indicates that the barrier materials are mostly transparent to the THz wave.

Considering that the sample may not be a single-component explosive but a mixture in the actual security inspection, based on the spectral data of known pure explosives components, Chen Y et al. proposed the THz spectral uncertainty analysis using micro genetic algorithm [101], by applying intelligent computing to the analysis and optimization of THz spectral combination. In this work, the mixture of benzoic acid, o-toluic acid and p-toluic acid were specifically analyzed. In 2015, Trofimov VA et al. proposed a method for the efficient analysis of explosives by pulsed terahertz spectroscopy using spectral dynamics [102]. In recent years, they have also developed an efficient tool to detect and identify substances in ternary explosive mixtures with similar spectral properties using broadband reflected THz signals [103].

In security applications, terahertz spectroscopy is used not only for the inspection of explosives, but also for the inspection of other contraband such as drugs [104, 105]. The THz images obtained after the analysis and processing of THz spectral information can also be used for the rapid detection of firearms and controlled knives [106–108]. As the application of terahertz spectroscopy technology for security screening technology continues to mature, more and more THz security inspection equipment began to put into practical application [25, 109].

Other Applications of Terahertz Spectroscopy

As we have already mentioned, terahertz spectroscopy can be used for non-destructive testing. We have also described its applications in biomedicine, security inspection, etc. This property can also be used for the detection of other substances and materials. In 2008, Jackson JB et al. used terahertz spectroscopy for the nondestructive examination of frescoes [110]. Subsequently, Abraham E et al. applied terahertz spectroscopy to the inspection of art paintings [26], and in 2015, Koch Dandolo CL et al. applied it to the inspection of panel paintings beneath gilded finishes [111].

THz fingerprints are available for pigments, adhesives and substrates of artworks, however, researchers still lack a database of THz spectra of these substances and materials, which makes the application of terahertz spectroscopy for artwork identification still difficult, and many researchers have set out to determine the THz spectra of different pigments. Li CY et al. in 2017 performed terahertz spectroscopy on several traditional Chinese pigments including cinnabar, red lead, oyster shell white, realgar, malachite, orpiment and azurite [112]. In 2019, Kleist EM et al. provided insight into the molecular and intermolecular forces that give rise to spectroscopy absorption features of crystalline copper-containing historical pigments in solid-state density flooding theory simulations and reveal deviations from simple harmonic vibrational behavior that may complicate these spectra, while investigating terahertz spectroscopy of solid azurite, malachite, and verdigris [113]. In the same year, Squires AD et al. analyzed phthalocyanine pigments under terahertz spectroscopy [114], while the identification and differentiation of copper phthalocyanines' α, β and ε crystal polymorphs is demonstrated. In 2021, Lee JE et al. performed terahertz spectroscopic analysis of vermillion pigments in freestanding and polyethylene mixed forms [115].

The aforementioned applications of terahertz spectroscopy are almost based on typical THz-TDS. Nevertheless, other types of terahertz spectroscopy have also been reported. In 2003, Kiwa T et al. used THz emission spectroscopy to check electrical faults in integrated circuits (IC), and the two-dimensional THz emission images of IC chips could be clearly observed [33]. In 2008, Dressel M et al. investigated the superconducting energy gap of superconductors using terahertz time-resolved spectroscopy [32]. They obtained terahertz spectroscopy of niobium and niobium alloys, magnesium diboride, and some organic and high-temperature superconductors to explore the inherent laws of superconductors.

Furthermore, terahertz spectroscopy can also be applied to building detection [28], energy power [116, 117], pharmaceuticals [118], food science [119], marine engineering [27], and other fields [120, 121].

METAMATERIAL-ENHANCED TERAHERTZ SPECTROSCOPY

In the previous section, we have talked about the great advantages of terahertz spectroscopy, nevertheless, the terahertz spectroscopy for substance detection also subjects to some limitations. The fact that the electromagnetic waves in the THz band have longer wavelengths compared to X-rays, for example. This means that their resolution and sensitivity is not high enough for detection of small samples and trace analysis when performing nondestructive testing. In order to solve these problems, researchers have carried out a lot of research.

One of the solutions is the application of THz metamaterials, which can enhance the interaction of the sample with THz wave, thereby improving the resolution and sensitivity of THz spectroscopic detection. Metamaterials are artificial structures composed of subwavelength unitary structures arranged and combined in a periodic or non-periodic form [122, 123]. In the design process, it is only necessary to design the parameters of its unit structure or change its spatial arrangement to realize desired extraordinary physical properties that cannot or are difficult to achieve with natural materials and traditional technologies, such as negative permittivity [124, 125], negative permeability [126, 127], negative refraction [128, 129], zero refraction [130], super absorption [131–133], super transparency [134, 135], etc. It is also possible to achieve arbitrary distribution of the medium parameters. In the application of THz spectroscopic detection, we make the resonance with THz waves appear as we need and enhance it by a rationally designed metamaterial unit structure. As early as 2004, Yen TJ et al. proposed a metamaterial that can be used for THz spectroscopic detection [136]. The use of metamaterials can greatly enhance the interaction between the small or even trace samples to be measured and the THz waves, thus making terahertz spectroscopy higher sensitivy for the detection of substances.

For the field of biomedicine, in 2016, Bui TS et al. used THz metamaterials as amplifiers to enhance the absorption signal of THz vibrations in the ultrathin adsorption layer of organic molecules, and on this basis, they detected protein macromolecules such as bovine serum albumin (BSA)

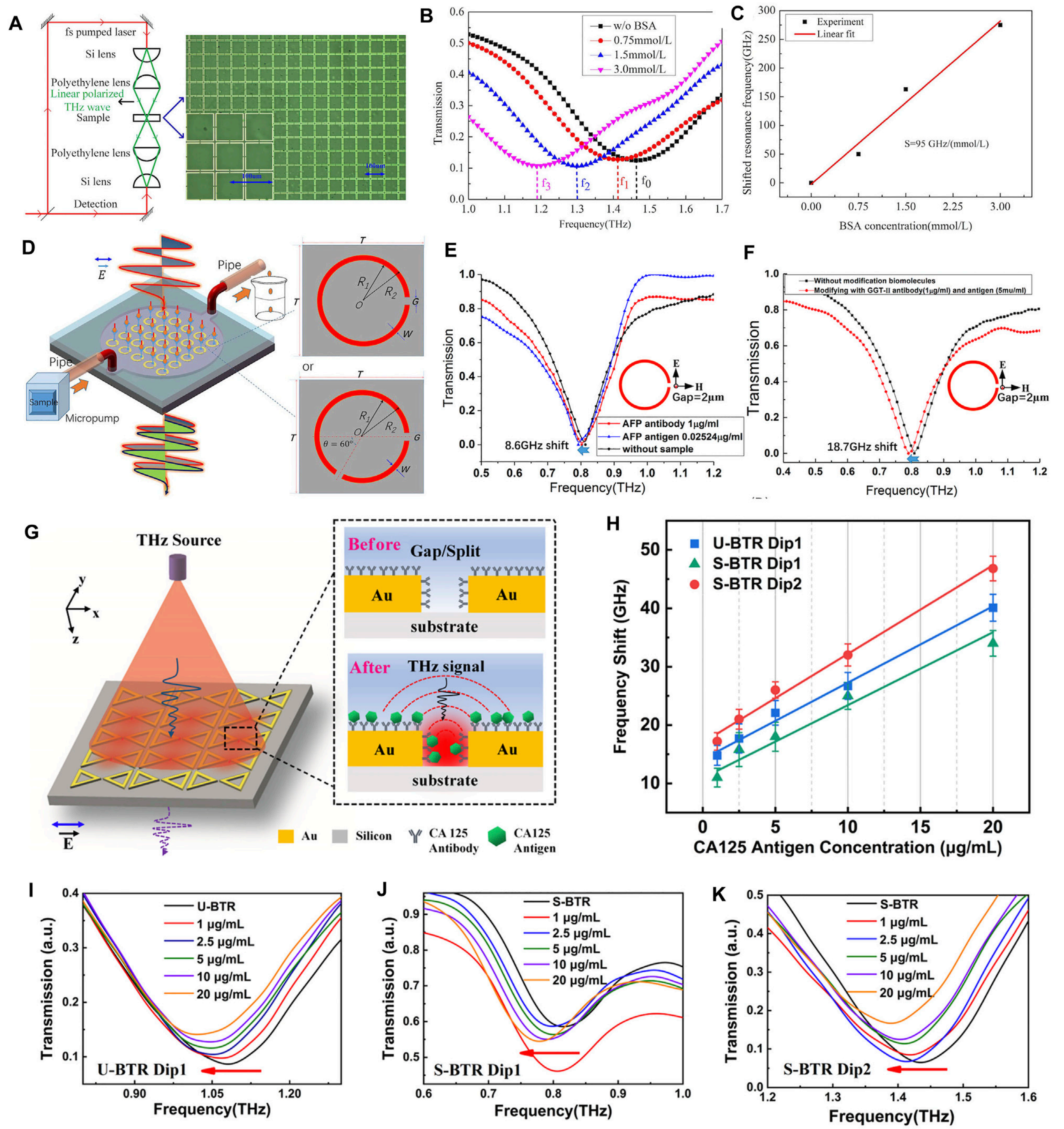

FIGURE 6 | (A) Experimental setup for THz spectral detection combined with metamaterials **(B)** THz transmission spectra of BSA solutions with different concentrations **(C)** Least squares fitting of experimental data of resonant frequencies to BSA concentrations [138]. Reproduced with permission. © 2016 IEEE. **(D)** THz metamaterials with integrated microfluidics for THz spectroscopic detection [140]. Reproduced under a Creative Commons Attribution 4.0 International License. © 2017 Springer Nature. **(E)** Transmission spectroscopy of liver cancer antibody AFP (1 μg/ml) and liver cancer serum antigen (0.02524 μg/ml) were detected using SRRs biosensors with a gap of 2 μm. The frequency shift of the transmission spectrum before and after injection of AFP antibody and serum antigen was 8.6 GHz [140] **(F)** The liver cancer biomarkers GGT-II antibody (1 μg/ml) and GGT-II antigen (5 μg/ml) were also detected by the same method. The transmission spectra were shifted by 18.7 GHz before and after injection of GGT-II antibody and antigen [140] **(G)** THz metamaterials for biomedical detection and the mechanism of reaction of their electric fields with analytes **(H)** Frequency shifts based on three dips for different concentrations of CA125 antigen and fixed concentrations (30 μg/ml) of CA125 antibody; transmission spectra of **(I)** U-bowtie triangle ring (BTR) Dip1 **(J)** S-BTR Dip1 and **(K)** S-BTR Dip2 at different concentrations of CA125 antigen [145]. Reproduced with permission. © 2021 American Chemical Society.

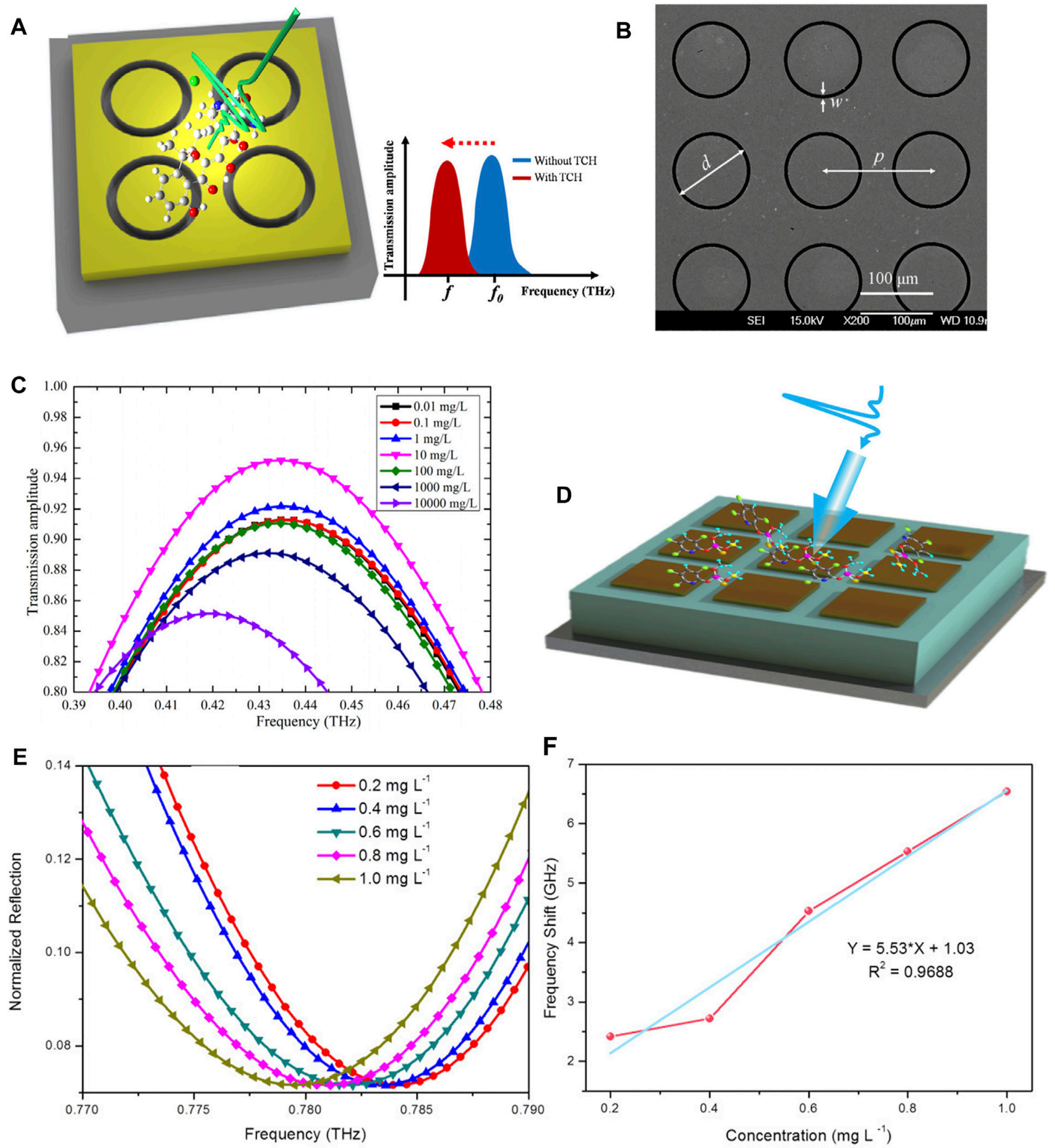

FIGURE 7 | (A) THz metamaterial for the detection of TCH and **(B)** its Scanning Electron Microscope (SEM) images **(C)** THz transmission spectra of TCH deposited on metamaterial detected at different concentrations [147]. Reproduced with permission. © 2016 Elsevier Ltd. **(D)** THz metamaterials for the detection of CM **(E)** THz reflectance spectra and **(F)** Frequency shift results of CM at different concentrations (0.2–1.0 mg/L), and the blue curve is a linear fit to the data [148]. Reproduced with permission. © 2017 Elsevier Ltd.

[137]. Wang S et al. designed a polarization-insensitive THz metamaterial for the detection of BSA [138]. The detection setup is shown in **Figure 6A**, and the measured data are displayed in **Figure 6B,C**. The black curve is the biosensor without BSA molecules, the red curve is 0.75 mmol/L, the blue curve is 1.5 mmol/L, and the pink curve is 3 mmol/L BSA solution. The corresponding resonance frequencies are 1.463, 1.413, 1.3, and 1.188 THz, respectively. This indicates that there is a red shift in the resonant frequency with increasing BSA concentration, and higher concentrations of biological analytes result in a corresponding increase in effective dielectric constant. The change in resonant frequency is

approximately linear with the BSA concentration, so the displacement of the resonance can be defined as a function of the change in BSA concentration. They obtained a maximum resonant frequency difference of 1.68 GHz with a minimum resolution of 17.7 μmol/L at full-angle range rotation. Another major challenge for the application of terahertz spectroscopy to biomedical detection is the strong absorption of THz waves in polar solvents such as water. In 2018, Tang M et al. overcame this difficulty by combining THz metamaterials with microfluidics to detect DNA oligonucleotides with base mutations [139]. Based on THz split resonant ring (SRR) metamaterials and microfluidics technology as shown in **Figure 6D**, Geng Z et al. detected alpha fetoprotein (AFP) and glutamine transferase isozyme II (GGT-II) as biomarkers for early hepatocellular carcinoma, and the detection results based on individual SRR gaps are shown in **Figure 6E,F** [140]. In 2019, Yan X et al. fabricated a THz metamaterial biosensor based on Fano resonance for the detection of cancer cells, with a theoretical sensitivity close to 455.7 GHz/RIU [141]. In 2020, Karmakar S et al. developed a stacked metasurface for solid matter, thin film, and chemical detection, where analytes can be detected between stacked metasurface that form Fano cavity [142]. Their study shows that broadside coupling can trigger much stronger near-field interactions and large-area interactions with substances leading to ultrasensitive sensing, capable of achieving >1 THz/RIU (= 1.76×10^5 nm/RIU) and a figure of merit of about 14.05 in the THz range. After the occurrence of COVID-19, Ahmadivand A et al. used THz metamaterials for the detection of SARS-CoV-2, and was able to detect SARS-CoV-2 stinger protein at femtomolar concentrations rapidly and accurately, which provided a more convenient and rapid method for the detection of COVID-19 [143]. Recently, Cui N et al. used THz metamaterial biosensors (see **Figure 6G**) to detect early cancer biomarkers carcinoembryonic antigen (CEA) [144] and breast cancer marker carbohydrate antigen 125 (CA125, results in **Figure 6H–K**) [145] both achieved good sensitivity. All of the above works indicate that the combination of metamaterials and terahertz spectroscopy has great potential in the future biomedical field.

As for agriculture and food production, we mentioned in the previous section that the researchers used terahertz spectroscopy to detect carbendazim, however, the data processing was complicated and the sensitivity was low. In order to improve the detection sensitivity, they further combined metamaterials to detect carbendazim [146]. The results showed that, the designed metamaterial can detect carbendazim down to 5 mg/L. Tetracycline hydrochloride (TCH) is a residue of antibiotics which is widely used in animals, and excessive residues in food can cause adverse effects on human health. Qin J et al. designed a THz metamaterial for TCH detection, as shown in **Figure 7A,B** [147]. The THz transmission spectra of TCH deposited on metamaterials were detected at different concentrations and the results were shown in **Figure 7C**. It shows the transmission spectra of the metamaterial as the TCH concentration varies from 0.01 mg/L to 10,000 mg/L. When the TCH concentration is lower than 0.1 mg/L, there is no significant difference in the transmission amplitude. It can be found that, due to the addition of metamaterials, their method can successfully detect TCH as low as 0.1 mg/L, and its sensitivity is greatly improved compared to the direct use of THz-TDS. In 2017, Xu W et al. applied metamaterials to the detection of chlorpyrifos-methyl (CM) [148]. In this experiment, the THz metamaterial works in reflection mode as shown in **Figure 7D**, and 10 μL of CM solutions of different concentrations are dropped onto the THz metamaterial and repeated three times. The THz reflection spectra of CM solutions at concentrations of 0.2–1.0 mg/L as well as the frequency shift results are shown in **Figure 7E,F**. It can be found from **Figure 7E** that the resonant peaks regularly shift to lower frequencies, and the value of the frequency shift increases with the increase of the CM concentration. Therefore, the frequency shift value should be a function of CM concentration, as shown in **Figure 7F**. We can observe a good linear relationship between the CM concentration and the frequency shift of the reflectance curve. Consequently, the detection limit of chlorpyrifos reached 0.204 mg/L after loading the THz metamaterial. The emergence of the good results is mainly due to the significant localized electric field enhancement effect of the surface excitation of the THz metamaterial. Subsequently, Nie P et al. designed an all-dielectric broadband THz metamaterial absorber for the detection of chlorpyrifos [133], increasing the detection limit to 0.1 mg/L. Their design has an interaction efficiency of 99% at 1.33 THz, with bandwidth covering a center frequency of 600 GHz, and the sensitivity and stability can be maintained under different temperature, humidity and time conditions. Recently, Liu J used THz metamaterials for the determination of organochlorine pesticide [149], Li B et al. combined terahertz spectroscopy with metamaterials for low-concentration nolosin detection [150].

CONCLUSION AND OUTLOOK

In conclusion, we overview the advantages offered by terahertz spectroscopy in the field of detection and identification of substances, such as biosafety, identification properties, penetration, coherence, high resolution, etc. In addition, with the introduction of metamaterials, terahertz spectroscopy can further improve its resolution and sensitivity to carry out the detection of micro or even trace substances.

At present, whether in biomedicine, security inspection or artwork identification, researchers are more likely to perform spectroscopic detection of specific substances. To advance the application of terahertz spectroscopy, a more extensive THz spectrum database of substances needs to be established. This will require more comprehensive investigations on various materials via terahertz spectroscopy in the future to supplement and improve the relevant data.

Besides, the strong absorption of THz waves by polar molecules such as water in the air remains an obstacle to the application of terahertz spectroscopy, and hence dry air or nitrogen purging or experiments under vacuum conditions are performed to eliminate this effect. However, such conditions are usually unavailable in large-scale practical applications, and this also limit the fast detection of substances. In addition, although we also mentioned that THz waves are penetrating, their penetration depth is still limited, especially when the sample is hidden behind an obstacle containing water. In the future, it is necessary to further optimize the structure of metamaterials, develop more new technologies similar to microfluidic channels, and propose newer data processing algorithms to more accurately describe the characteristics of terahertz spectroscopy of substances. Additionally, it is also necessary to further reduce the cost of THz technology, increase the detection limit, and further improve the resolution and signal-to-noise ratio of instruments. Overall, terahertz spectroscopy technology has been showing more and more significant potential for application in the detection and recognition of substances.

AUTHOR CONTRIBUTIONS

XF and TJC: supervision, preparation, and revision of the manuscript. YL wrote the first draft of the manuscript. QC and YF contributed to the preparation of the manuscript. All authors approved the submitted version.

FUNDING

This work was supported in part by the National Key Research and Development Program of China (Grant Nos. 2018YFB1801505, 2017YFA0700201, 2017YFA0700202, and 2017YFA0700203), in part by the National Natural Science Foundation of China (Grant Nos. 61871127, 61735010, 61731010, 61890544, 61801117, 61722106, 61701107, 61701108, 61701246, and 61631007), and in part by the 111 Project (Grant Nos. 111-2-05).

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