Harnessing The Self-Healing Effect of Terahertz Rays: Advancements and Applications

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***Abstract*—Terahertz (T-rays) radiation is gaining attention in medical applications due to its potential for self-healing effects. This abstract explores T-ray technology's recent advances in biomedical engineering. T-rays, falling between infrared and microwave radiation, can activate self-healing mechanisms in damaged tissues, promoting cell regeneration, wound healing, and implant integration. Semiconductors, like quantum cascade lasers, generate T-rays through nonlinear optical frequency mixing. In summary, T-rays offer promise for material restoration and repair, with applications in biomedical engineering, enhancing device reliability and tissue regeneration. Research and technological advancements may revolutionize various industries with self-healing capabilities.**

I. Introduction

A. An overview of Terahertz radiation (THz)

1) What is THz?: In the electromagnetic spectrum, terahertz radiation is situated between microwave and infrared radiation, and it has certain characteristics in common with both of these radiation types. Terahertz radiation is non-ionizing and moves in a line of sight. Terahertz radiation, like microwaves, may pass through a broad range of non-conducting materials, including plastic, ceramics, stone, paper, cardboard, clothes, and wood. Generally speaking, the penetration depth is lower than that of microwave radiation. Terahertz radiation, like infrared, cannot pass through liquid water or metal and only partially passes through clouds and fog. [1]

In the field of physics, terahertz radiation, also known as submillimeter radiation, terahertz waves, T-rays, T-waves, T-light, T-lux, or THz, encompasses electromagnetic waves with frequencies ranging from 0.3 to 10 terahertz (THz). This term is used for electromagnetic radiation falling between 300 GHz, the high-frequency limit of the millimeter wave band, and 3000 GHz, the low-frequency limit of the far-infrared light band. The associated wavelengths in this range vary from 1 mm to 0.1 mm, as illustrated in Figure 1. [2] Terahertz radiation is often referred to as the submillimeter band because it starts at a wavelength of 1 mm and extends to shorter wavelengths. This band is also recognized for its application in astronomy, where the radiation is commonly referred to as submillimeter waves.

2) Self-healing effect using Terahertz waves: The use of THz radiation to elicit particular cellular responses that can expedite self-healing mechanisms is one of the most promising lines of inquiry [5]. THz waves, for example, might be used to stimulate and guide stem cells, encouraging them to regenerate tissue, providing a new way to treat wounds or degenerative illnesses. Additionally, by utilizing these waves to control the inflammatory response, chronic inflammatory disorders may be less severe and inflammation may resolve more quickly. [6] Through the manipulation of biological mechanisms like migration, proliferation, and gene expression, THz technology holds the potential to transform wound healing by reducing scarring and enhancing tissue restoration.

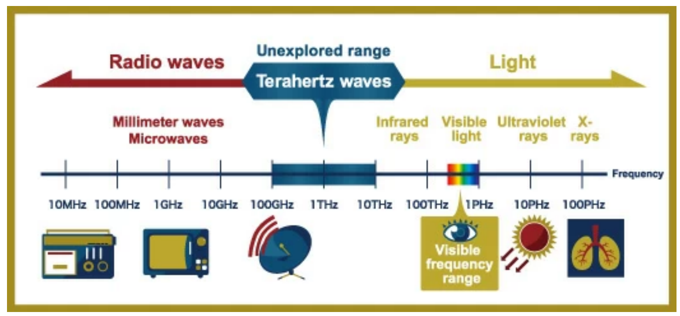

Fig. 1. Frequency range of Terahertz(THz) waves [3]

Furthermore, because THz radiation is non-destructive, it may be used to monitor tissue characteristics and cellular changes in real time, providing medical professionals with important new information. THz imaging, for example, can be used to monitor the status of wound healing without interfering with the healing process, or to evaluate the viability of donated organs. [7]

The potential applications of self-healing using THz waves extend beyond localized treatments. Researchers are exploring how these waves could be employed in targeted drug delivery systems, using THz radiation to trigger the release of therapeutic compounds at precise locations within the body. This could revolutionize drug administration, minimizing side effects and optimizing treatment outcomes.

B. Motivation and Contribution

1) Motivation: The concept of self-healing using Terahertz (THz) waves represents a fascinating frontier in scientific exploration and medical research. Terahertz waves, situated between the microwave and infrared regions of the electromagnetic spectrum, exhibit unique properties that make them a promising candidate for various applications, including medicine. One particularly intriguing area of investigation involves leveraging THz waves to stimulate self-healing within the human body. This innovative approach capitalizes on the ability of THz waves to penetrate biological tissues without causing harm, interacting with biomolecules and cellular structures in a non-invasive manner. By harnessing THz technology, scientists aim to promote and enhance the body's inherent healing mechanisms, potentially accelerating tissue regeneration, reducing inflammation, and aiding in the repair of damaged cells and organs. This research holds the promise of transformative advancements in healthcare, paving the way for less invasive and more effective treatments, and ultimately offering hope to individuals grappling with a wide array of health challenges.

2) Contribution: The development of a product harnessing the power of an infrared laser and a nonlinear crystal represents a significant advancement in modern technology. This innovative pairing opens up a realm of possibilities in various fields, from telecommunications and spectroscopy to medical diagnostics and materials science. By skillfully manipulating the properties of the nonlinear crystal and the precise characteristics of the infrared laser, our team has unlocked the potential to generate terahertz waves, a particularly valuable wavelength range for its non-ionizing and non-destructive properties. This novel product promises to revolutionize industries, offering solutions in the realms of imaging, security scanning, and molecular identification, among others. The fusion of advanced laser technology and nonlinear optics has paved the way for this groundbreaking product, marking a notable stride toward addressing complex challenges across diverse sectors and offering a valuable tool for scientific discovery and practical applications.

II. THz and Skin Cells

A. *Effects of THz Radiation on the Skin*

The effects of THz radiation on biological cells, tissues and organisms have been important since the creation of THz sources, but this has not yet been fully studied. For example, the safety limits on energy density set by the International Commission on Non-Ionizing Radiation Protection are not established for frequencies above 300 GHz [8]. Studies performed show that THz radiation can have both thermal effects [9] [10] (involving heating of exposed objects due to absorption) and non-thermal effects on biological objects. Like other electromagnetic waves, THz heats biological tissues and the degree of heating depends on the applied power, while the strong absorption ability of water is an important factor participating in the heating process. The ability to heat tissue using THz waves has been demonstrated in several modeling studies. [11] [12] However, such heating is associated with CW radiation sources and high power densities, whereas for pulsed sources the average power is usually too low to cause noticeable changes.

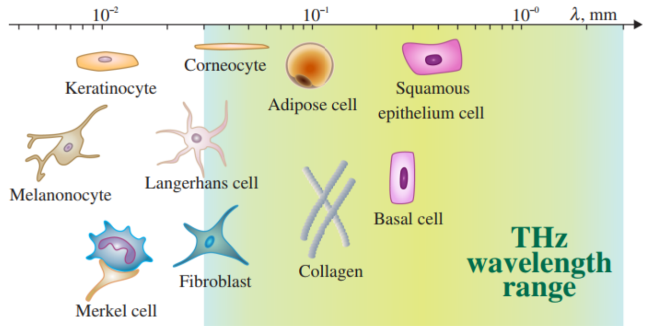

Fig. 2. Comparison of typical skin components with the THz wavelength ranging from 0.03 to 3 mm. Courtesy of I. N. Dolganova.

Another type of effect is related to non-thermal mechanisms of THz waves—biological system interactions. Supposedly, THz radiation can produce linear or non-linear resonance effects at the molecular level, especially in deoxyribonucleic acid (DNA), where local hydrogen bond disruption can lead to modify gene expression. [13] [14] [15] Therefore, THz radiation can serve as a convenient and effective tool to modulate cellular activity. On the one hand, most of the THz intensities used are not harmful to cells and do not cause any deterioration in their ability to exist. [16] Studies performed on skin cells showed no signs of apoptosis and oxidative stress. [17] On the other hand, there are data regarding THz-induced adipogenic differentiation of melanoma MSCs and indications that THz may influence protein transcription. The ECM composition of the skin can be indirectly affected by changes in cellular activity with THz radiation. For example, wound healing is stimulated by TGF-induced collagen synthesis after irradiation. This finding suggests the potential application of THz radiation in skin regeneration.

B. *THz exposure of the mouse ear skin in vivo*

In the experiment of mouse ear skin, broadband pulsed THz radiation was administered on keratinocytes of mouse's dorsal skin in vivo for 1 hour. Particularly, the THz radiation had a spectral range of 0.1-2.5 THz. According to genome-wide analysis, there were changes/alterations in 149 genes, which play a role in growth, healing, organogenesis and cell migration. Gene expressions of THz exposed subjects also demonstrate some differences compared to those with UV and neutrons, as shown by bioinformatic examination. Moreover, THz-induced changes in gene expression patterns are concluded to be comparable/equivalent to those caused by wounds/injuries. [19]

In another test, the skin was exposed for 30 minutes to a 2.7 THz central frequency with a 3 Hz repetition rate, 4-μs pulse and a 260-mW/cm2 average irradiance.The schematic diagram for this test is displayed in Figure 3. Observations of the diagram demonstrated acute inflammatory response. In comparison, an IR camera found no temperature change of the skin due to THz radiation exposure. [20]

Based on this result, it appears that such an acute inflammatory response can be triggered without THz radiation disrupting the skin's structure. THz exposure for living cells in vivo, however, can induce unexpected dynamic responses, which cannot be replicated in simplified in-vitro tests. [20]

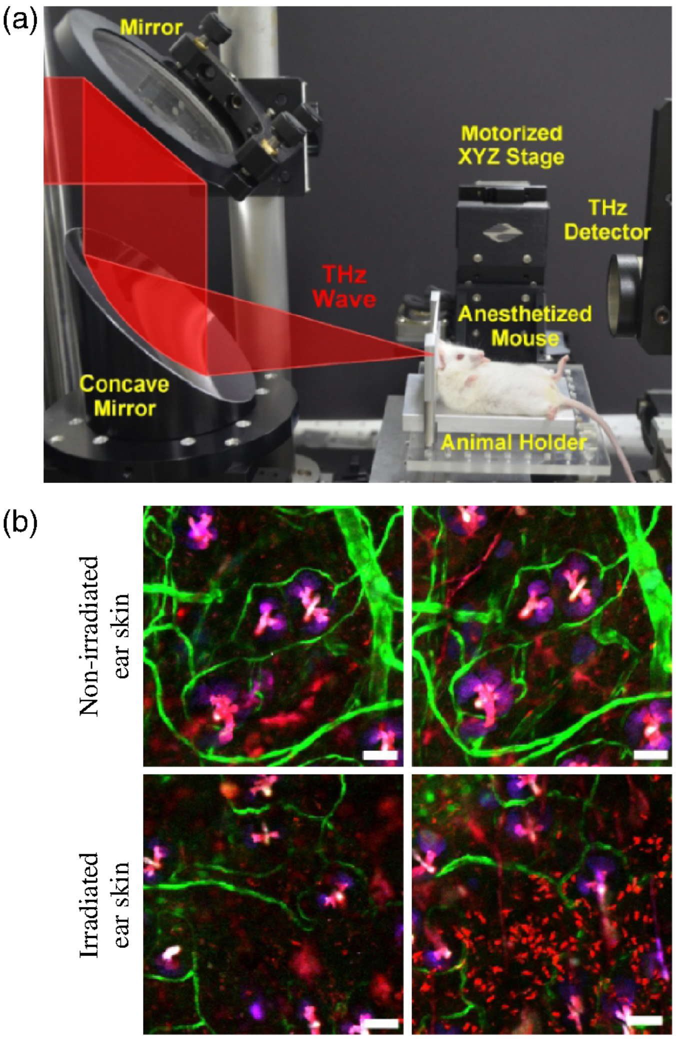

Fig. 3. Hz exposure of the mouse ear skin in vivo. (a) A photo of the THz setup. A living anesthetized mouse is placed on an animal holder that is fixed at a motorized 3D translation stage. (b) Distribution of neutrophils in the mouse ear skin before and after the THz exposure: Gr-1 + neutrophil (in red), Tie2 + blood vessel (green), and autofluorescent hair follicle (magenta) [20]

III. Terahertz Advancement and Application

A. THz production procedure using infrared laser and nonlinear crystal (Cost-Effective)

A variety of techniques to generate and detect THz radiation have been developed in the past few decades, and these form the basis of the spectroscopic and imaging instruments. [18] Among the existing schemes, generating terahertz waves using an infrared laser transmitter and lithium niobate (LiNbO3) crystal is a task involving advanced optics and materials science which can reduce the production cost of terahertz wave. In the first stage, using a high-power continuous-wave (CW) or pulsed infrared laser source with a wavelength in the near-infrared range, typically around 800 nm to 1550 nm, to premiered to long lens with concave reflector, LiNbO3, and convex mirror as demonstrated in Figure 3. In this stage, the pump beam and signal beam are directed into the LiNbO3 crystal, then inside the crystal, the nonlinear DFG process occurs, where the two input beams interact to generate a terahertz wave through a process called parametric down-conversion. The frequency of the generated THz wave is determined by the difference in frequencies between the pump and signal beams. A suitable optical system is used to extract the generated terahertz wave from the LiNbO3 crystal. At the final stage, the generated terahertz wave can be detected and analyzed using specialized terahertz detectors and spectrometers for various applications. The THz wattage can be change by changing the wattage of the transmitter.

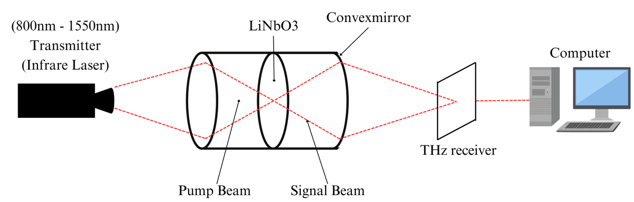

Fig. 4. Terahertz (THz) waves generation procedure

B. Advancement on generating terahertz rays using femtosecond laser

Recent advances: Optoelectronic THz time-domain system successfully served in pioneering THz imaging experiment. [21] Originally, terahertz time-domain systems were large and primarily used in scientific laboratories. However, their sensitive detection capability, relying on phase-locked detection, made them effective despite relatively low emission powers, typically below 1 µW. Traditional systems based on Ti:sapphire lasers were also bulky and required complex optical pumping schemes for operation. To make these systems more compact, energy-efficient, and user-friendly, researchers explored the use of ultrafast fiber laser-based systems. However, this shift led to challenges with low-temperature grown GaAs, as it was no longer suitable for terahertz generation and detection due to changes in the excitation wavelength. This prompted efforts to develop materials with short carrier lifetimes and high dark resistivities. One early solution was the adoption of InGaAs/InAlAs photoconductive layers, which significantly improved emission power, dark current, and receiver sensitivity compared to conventional planar antennas. [22] They were applied for continuous wave THz generation at 1.5 µm [23] optical pumping and in TDS using 1 µm wavelength excitation. [24] However, the structures, consisting of 100 periods of InGaAs/InAlAs, were complex and costly for the intended purpose. An alternative approach emerged with ternary GaAsBi structures initially employed for THz detection in a TDS system using p-InAs as the THz emitter. [25] Subsequently, a TDS system was showcased utilizing Yb:femtosecond lasers, exclusively incorporating GaAsBi materials for both emission and detection. [26] Due to the intrinsic p-type growth of GaAsBi, it was unsuitable for 1.55 µm wavelength excitation. To address this limitation, molecular beam epitaxy (MBE) synthesis proposed and successfully demonstrated the intrinsic n-type InGaAs alloyed with Bi content (refer to Figure 5) in a TDS system employing 1.55 µm pulses from an Er-doped fiber laser. [27] The system exhibited a frequency limit of 4.5 THz, a 65 dB SNR ratio, and an emission power of 5 µW. These investigations underscored the importance of meticulous materials design for effective THz emission across diverse TDS systems.

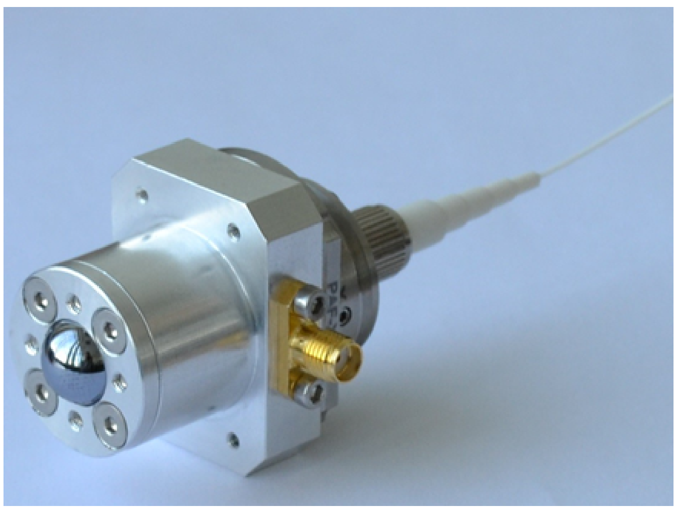

Fig. 5. Photo of fiber-coupled optoelectronic GaAsBi-based THz emitter mounted with a silicon lens. Courtesy of Laboratory of Ultrafast Optoelectronics Laboratory at Optoelectronics Department at FTMC and Teravil Ltd., Vilnius, Lithuania. [29]

A recent study has introduced a promising strategy involving the use of molecular beam epitaxy (MBE)-grown rhodium (Rh)-doped InGaAs, showcasing a unique combination of ultrashort trapping time, high electron mobility, and high resistivity. [28] Due to these distinctive characteristics, terahertz emitters linked to optical fibers have demonstrated exceptional performance. They have successfully generated significant terahertz power, reaching levels as high as 637 µW. The bandwidth extends up to 6.5 terahertz, and they have achieved an unprecedented peak dynamic range of 111 dB.

C. THz range equation effectiveness

The effective medium theory postulates that at the THz-wavelength scale, tissues are considered uniform, and it characterizes the interactions between THz waves and tissues by utilizing models that represent their effective dielectric response. These models define both the frequency-dependent real part ε' and the imaginary part ε'' of a complex dielectric permittivity concurrently. Alternatively, it defines both the real part n' and the imaginary part n'' of a complex refractive index.

$$\tilde{\varepsilon} = \varepsilon' - i\varepsilon'' \tag{1}$$

$$\tilde{n} = n' - in'' \equiv n - i\frac{c}{2\pi\nu}\alpha \equiv \sqrt{\tilde{\varepsilon}} \tag{2}$$

where $c \simeq 3 \times 10^8$ m/s is the speed of light in free space, and α is an absorption coefficient (by field) in cm^{-1}.

D. THz therapy

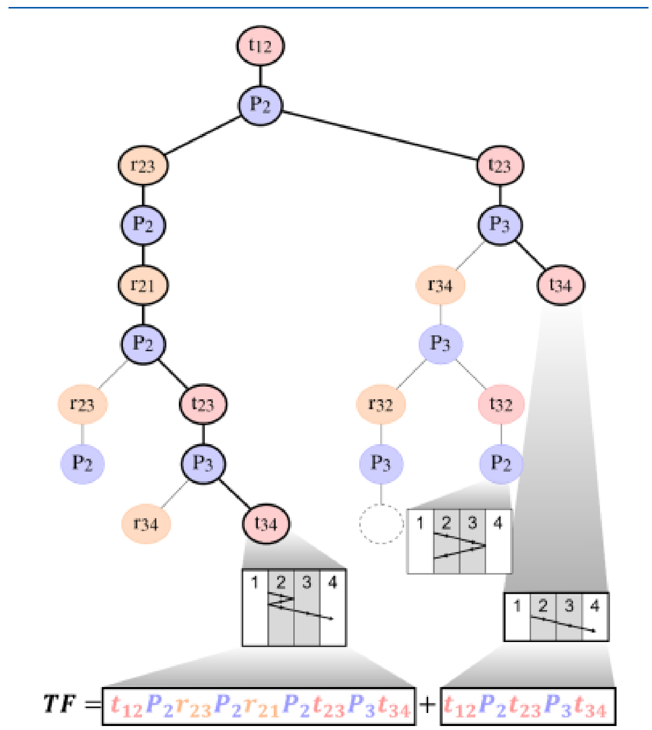

Fig. 6. The tree structure, which is used to enumerate all the paths the pulse can take through a two-layer sample. These paths are then summed to construct the full transfer function. Each node represents a transmission, reflection, or propagation event, for example, tij presents transmission at the interface between layers i and j. Each inset shows the path represented by the corresponding node. The empty dashed node shows one of the places where the tree building process has been terminated by a time or amplitude cutoff at that node. The expression at the bottom gives the transfer function (TF) that this tree would yield [30]

THz-TDS systems measure the sign-resolved electric field of a THz pulse as a function of time. A typical experiment consists of two measurements: a pulse passed through the sample of interest and a pulse passed through a well-characterized reference or blank substrate material. The dielectric properties of the sample can then be extracted by comparing the two resulting pulses [30]. Specifically, we calculate the change in each frequency component's amplitude and phase by Fourier transforming each pulse and taking the complex ratio of the two. This quantity is referred to as the transfer function (TF) and is defined as TF(ω) = E (sample) / E (reference), where E (sample) and E (reference) are the complex-valued

Fourier-transformed spectra of the sample and the reference, respectively, and ω is the angular frequency. [30]

Frequency	Irradiance (mW/cm^2)	Exposure time	Object	Elfects
Broad spectrum centered at 10THz	1	2, 6, 9 h	Mouse MSCs	Exposure of cells to THz radiation for 9 h caused changes in gene expression, whereas in response to shorter duration of exposure, the changes were less pronounced. The lipid inclusions that are a characteristic sign of MSC differentiation into adipocytes were clearly visible after 9 h of exposure.
1) 2.52THz; 2) 10THz	1.2	1) 2 h 2) 2, 12 h	Mouse MSCs	It was found that genes affected by prolonged irradiation are characteristic for already differentiated cells, Le., for adipocytes, whereas genes differentially expressed after short (2 h)THz irradiation are characteristic of pluripotent stem cells.
1) 10THz 2) 2.52THz	1.2	1) 2 h; 2) 9 h	Mouse MSCs	1) The level of expression of the shock protein genes remains unchanged after 9 h of THz irradiation. 2) The level of the stress-responsive CRP gene that is activated in dying cells remains low in both the control and irradiated cells suggests the absent cellular stress response.
0.14THz	10, 30, 50 70 , and 100	20 min	hDF	120 h after the irradiation, the proliterative activity of the irradiated cels did not differ from the non-irradiated control. The level of NO production by irradiated fibroblasts did not differ from the NO level of non-irradiated cells. The 0.14-THz radiation of 10 - to 100−-mW power did not affect the functional activity of human skin fibroblasts.
0.15THz	0.4	20 min	hDF	1) No effect on cell cycle; 2) no effect on heat shock response; 3) increase in genome damage; 4) no effect on clastogenic genome damage; 5) no effect on telomere length; the THz radiation exposure in vitro caused non-thermal effects on the genome.
2.52THz	84.8	5, 10, 20 40, or 80 min	hDF	Celular temperatures increased by 3°C during all THz exposures. At the used power, radiation at 2.52THz can generate thermal effects in mammalian cells.
0.14THz	10, 30, 50 70, and 100	20 min	hDF	After exposure to THz radiation, the prolferative activity of the irradiated cells did not differ from the control. The level ot NO production by irradiated fibroblasts did not differ from the control.
0.38 and 2.52THz	0.03 to 0.9	2 and 8 h	hDF, HaCaT cells	No DNA damage was found in HaCaT and hFB cells after irradiation.
0.10 to 0.15THz	0.4	20 min	hDF	The THz irradiation resulted in the genome damage in hDFs. No changes in the expression of proteins associated with DNA damage sensing and repair were detected, indicating that THz radiation exposure may affect genome integrity through aneugenic effects.

Fig. 7. Effect of THz on Skin cell [18]

IV. Conclusion

In this paper, we've outlined recent advancements in Terahertz (THz) technology pertaining to skin analysis, and diagnosis. We've highlighted how THz imaging and spectroscopy offer unique insights into skin tissue characteristics. While there have been significant developments in understanding THz interactions with biological tissues over the past few decades, certain limitations still hinder widespread adoption.

Fortunately, for skin analysis, the limitations associated with the limited penetration depth of THz radiation are less pronounced, although they become more critical for deeper skin layers. The development of compact and affordable THz sources remains a challenge. Spatial resolution is constrained by diffraction limits, limiting single-cell detection, although promising techniques like THz solid-immersion microscopy show potential for biomedical imaging.

Improvements in signal enhancement, contrast, sensitivity, and signal analysis will aid detection tasks. Moreover, THz-based distinction between normal and pathologically altered skin, without the need for contrast agents, proves valuable for in vivo applications. Research into biological effects induced by THz radiation is ongoing. Low-power THz radiation can influence gene expression, offering potential applications in skin tissue regeneration and cancer treatment. However, the effects of high-power THz radiation and its application in cancer cell destruction require further study. Recent THz technology advancements, especially in skin tissue studies, highlight their potential as both research and therapeutic tools.

Acknowledgment

We acknowledge the profound impact of Terahertz (THz) radiation on skin cells, which has opened new avenues in understanding their behavior and potential applications in skin-related research and therapies. THz technology has revealed valuable insights into skin tissue analysis, regeneration, and even cancer treatment. We appreciate the ongoing research and its potential to revolutionize our approach to skin health and medical treatments.

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