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Review

Millimeter waves in medical applications: status and prospects

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A R T I C L E I N F O

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A B S T R A C T

Millimeter waves are electromagnetic waves with wavelengths of 1–10 mm, which have characteristics of high frequency and short wavelength. They have gradually and widely been used in engineering and medical fields. We have identified studies related to millimeter waves in the biomedical field and summarized the biological effects of millimeter waves and their current status in medical applications. Finally, the shortcomings of existing studies and future developments were analyzed and discussed, with the aim of providing a reference for further research and development of millimeter waves in the medical field.

1. Introduction

The microwave is an electromagnetic wave in the frequency range of 300 MHz–300 GHz, with high frequency, short wavelength, and certain penetration, and is widely used in many fields such as communication, the military, and medicine. Millimeter waves, as part of the microwave category with a wavelength of 1–10 mm, are located in the wavelength range where microwaves and far-infrared waves overlap and thus have the characteristics of both wave spectra. Its corresponding frequency is 30–300 GHz, which developed rapidly after the 1950s. The wide operating bandwidth of millimeter waves do not easily generate frequency band interference, while its narrow beam can be used for high-resolution precision detection [1]. Figure 1 shows the different frequency bands of electromagnetic waves classified according to their frequency magnitude.

With the increasing use of millimeter waves in engineering and technology, their biological effects are also receiving much attention from researchers. Previous studies have reported many in vivo and in vitro millimeter wave biological effects and studies on the therapeutic effects of millimeter waves. Since the 21st century, as a non-contact sensing technology, millimeter wave radar sensors have been widely used in the field of autonomous driving due to their advantages, such as accurate sensing without interference [2]. With the development of the market and the constant maturity of the technology, these waves have also shown a broad potential for application in the medical and healthcare field. This review summarized the applications of millimeter waves in biomedical fields, including their biological effects, medical applications in the diagnosis and treatment of diseases, and in the detection of vital signs (Figure 2).

2. Biological effects of millimeter waves

2.1. Thermal effects

The biological effects of millimeter waves on living organisms can be divided into thermal and non-thermal effects. A certain frequency and intensity of electromagnetic waves applied to a living body can produce a thermal effect that increases the local or overall temperature. The biothermal effect of millimeter waves is related to the large amount of water molecules in the organism. The impact of certain energy of millimeter waves on the water molecules in the organism leads to an increase in their irregular motion and, thus, to a thermal effect. Due to the short wavelength of millimeter waves and poor penetration ability, the resulting biothermal effect is mainly achieved in the skin, cornea, and other areas with superficial and high water content [3].

The effect of millimeter waves on living organisms is different from that of the general microwave. Due to its high frequency, microwave energy is concentrated in a very thin area of the body surface, resulting in the thermal effect on the skin, cornea, and other parts of millimeter waves. The millimeter wave is an electromagnetic wave, and its radiation intensity (power density) is positively correlated with the frequency of the electromagnetic wave per unit time. Previous studies have discussed the thermal effects of common millimeter waves in different frequency bands and explored the power density of millimeter wave

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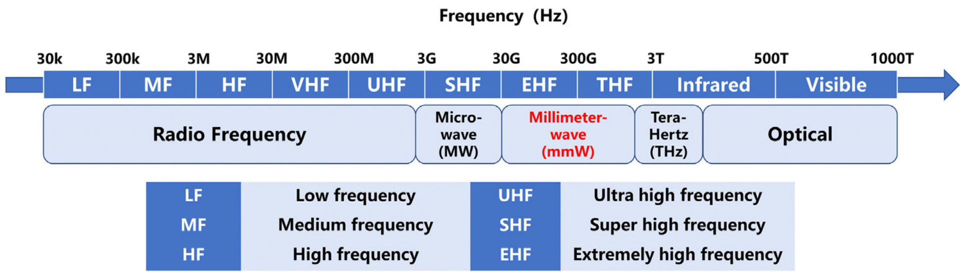

Figure 1. Classification of frequency of electromagnetic waves in frequency.

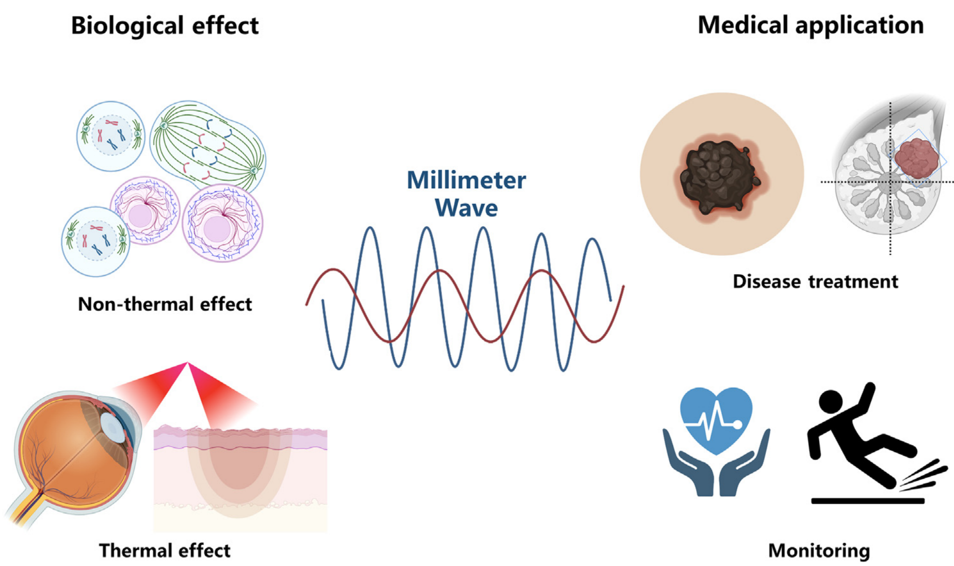

Figure 2. Applications of millimeter waves in biomedical fields.

irradiation at different frequencies to produce thermal effects on living organisms, providing a reference for further applications of millimeter waves. Ryan et al. [4] found in their experiments that millimeter waves penetrate to a shallow depth, allowing most of the energy and heat to be deposited between 1 and 2 mm of skin. Blick et al. [5] studied the threshold for human skin to feel heat under millimeter wave irradiation, and reported values of only 4.5 mW/cm^2 for the 95 GHz millimeter wave and 8.84.5 mW/cm^2 for the 35 GHz millimeter wave. Walters et al. tested the nociceptive threshold of 94 GHz millimeter wave irradiation on human skin. When the irradiation time was fixed at 3 s, the threshold power density at which a person felt pain was 1.25 W/cm^2, and the average temperature at which stinging pain was produced was 43.9 ± 0.7 °C [6]. Alekseev et al. [7] showed that the skin temperature in the forearm area was higher compared to the finger with greater blood flow in bioheat transfer equilibrium experiments, suggesting that the millimeter wave effect of the skin heat may be influenced by blood flow. Another study discussed the impact of blood flow on the thermal effects of the skin produced by irradiation by the 94 GHz millimeter wave by blocking forearm blood flow [8]. Nelson et al. [8] studied the millimeter-wave-generated skin thermal effects between different species, using a 94 GHz millimeter wave for high-power short-time and low-power long-time irradiation on the skin of rats, macaques, and humans, respectively. Under high power density (1 W/cm^2), short time (4 s) irradiation conditions, changes in skin blood flow had no effect on the rate of millimeter wave-induced temperature rise. In contrast, under low power density (175 mW/cm^2) and prolonged (180 s) irradiation conditions, altering skin blood flow significantly affected the rate of millimeter wave-induced temperature rise [9]. These studies suggest that there are differences between species in millimeter wave thermal effects and that skin blood flow during prolonged irradiation is an important factor that affects millimeter wave thermal effects. A dynamic blood flow model incorporating thermoregulatory mechanisms has been proposed to better describe the thermal cutaneous impact of millimeter wave irradiation.

Given the similarities to the human corneal structure, rhesus monkeys were used as a model to study the corneal damage effects of millimeter waves. Slit lamp examination, corneal morphology, and specular microscopy were performed after millimeter wave irradiation. The corneal damage thresholds for 35 GHz and 94 GHz millimeter waves were 7.5 J/cm^2 and 5 J/cm^2, respectively, determined by corneal epithelial cell edema and fluorescein staining. This damage was recovered 24 h after irradiation and no significant changes in endothelial cell counts were observed [10–11]. A recent study discussed the effect of blinking on the thermal effect of millimeter wave corneas on this basis. It indicated that the damage threshold should be increased to 20 W/cm^2 if the interrupting effect of blinking on irradiation is considered [12]. In addition, the effects of low-dose 60 GHz millimeter waves on the eyes were studied. Irradiation of rabbit and monkey eyes with millimeter waves at a power density of 10 mW/cm^2 did not cause corneal cell damage, changes in iris vascular permeability, or crystal clouding in single continuous irradiation for 8 h or 4 h/day for 5 days, indicating that millimeter waves at this condition do not cause eye damage [13]. Interestingly, studies are applying the thermal effect of millimeter waves for in situ cell isolation, whereby cells are detached from the culture dish by localized and rapid irradiation of the plate with a 94 GHz millimeter wave radiation source, which causes the liquid to absorb and produce a thermal effect and kill the cells at a specific location. In another studies, cells were fixed directly in situ by thermal effects and did not affect subsequent assay experiments on cells [14].

2.2. Non-thermal effects

Non-thermal effects have been suggested as the mechanism that triggers biological effects such as genotoxicity, cell proliferation, gene expression, cell signaling, and membrane function [2]. Unlike the superficial limitations of thermal effects, some researchers have found that such non-thermal effects can occur at deeper or more distant parts of the organism, producing a depth-penetrating effect. The coherent resonance of electromagnetic waves generated by millimeter wave irradiation is considered the main possible mechanism for non-thermal effects. When the millimeter-wave vibration frequency is close to that of molecules such as cell membranes, organelles, and nucleic acids in living organisms, a series of biological effects may be triggered, which may affect the functions of tissues, organs, and cells of living organisms [15]. There is evidence that millimeter waves act by elevating Ca^{2+} levels to activate voltage-gated calcium channels and voltage-gated potassium channels [16]. The medical applications of millimeter waves are mainly based on the non-thermal effects.

2.2.1. Cellular functional activity

Many studies have been conducted to investigate the effects of millimeter waves on cell proliferation, function, and activity. Cohen et al. [17] continuously exposed *E.coli* cells to 99 GHz millimeter waves for 19 h. *E.coli* cell proliferation increased slightly compared to the control group but the difference was not statistically significant. Hovnanyan et al. [18] reported that low-intensity millimeter wave irradiation at 51.8 GHz and 53 GHz inhibited the growth of *E.hirae* ATCC 9790 bacteria, regardless of the length of exposure time. Soghomonyan et al. [19] found that millimeter wave irradiation (51.8 GHz and 53 GHz) inhibited *Lactobacillus acidophilus* proliferation and enhanced the bacteriostatic effect of ceftazidime, probably due to its effects on cell membrane and enzyme activities. Similarly, a study by Torgomyan et al. reported similar findings for the same frequency of irradiation of bacteria [20]. Beneduci et al. [21] found that 53–78 GHz millimeter waves have growth inhibitory effects on leukemic K562 cell lines, which can be attributed to loss of intracellular homeostasis in irradiated cell systems and stimulation of defense repair mechanisms, leading to increased intracellular energy metabolism, which affects cell proliferation. In the study by Yaekashiwa et al. [22], the non-thermal effects of millimeter wave irradiation at 70–300 GHz on cell proliferation and activity of human skin fibroblast cells (NB1RBG) and human glioblastoma (A172) were evaluated following exposure to a millimeter wave irradiation source with a wide range of adjustable frequencies in frequency increments of 1 GHz. The intensity of irradiation was controlled below 10 μW to avoid thermal effects, and no changes in cell proliferation or activity were detected. Imre et al. [23] analyzed the effects of millimeter wave irradiation of low power at a frequency of (61±2.1) GHz on epidermal keratinocytes by measuring chemokine release, heat shock protein (Hsp) production, cell viability, and intercellular gap junction communication, and there was no evidence of deleterious effects of irradiation on epidermal keratinocytes. Furthermore, some researchers found that 42 GHz millimeter wave irradiation in the nasal region of mice upregulated natural killer (NK) cell functional activity [24]. Overall, different studies have reported the effects of millimeter waves on cell proliferation and activity, but there are still no consistent conclusions, the reasons for which may be related to the variability of cells, radiation sources, radiation time intensity, and experimental environments used in different studies, suggesting that the accurate determination of the irradiation dose in subsequent relevant investigations must be rigorously analyzed for specific experimental conditions.

2.2.2. Genetic biological effects

The genetic and biological effects of millimeter wave radiation have been evaluated in cells, including their impact on gene expression, genotoxicity, and chromosome morphology. Koyama et al. exposed human corneal epithelium (HCE-T) and human lens epithelium (SRA01/04) cells from human eyes to 60 GHz millimeter wavelength radiation for 24 h and evaluated micronucleus formation, DNA breakage, and Hsp expression in cells by controlling the temperature increase below 0.1 °C to avoid thermal effects. The results did not show a significant effect of millimeter waves on the genotoxicity of these cells [25]. Le Quément et al. [26] used genomic microarrays to study the effects of low-power millimeter wave irradiation on genomic expression in human keratinocytes and found that five genes produced transient expression modifications after 6 h of continuous irradiation with a 60 GHz radioactive source. Changes in dermal gene expression profiles and histology after exposure to 35 GHz radiofrequency radiation have been studied. Rats were exposed to 35 GHz millimeter waves at 75 mW/cm^2, and skin samples were collected for genetic analysis after 6 h and 24 h. Up-regulation of genes related to oxidative stress, immune response, and tissue matrix turnover in different exposure periods occurred, suggesting that prolonged exposure to 35 GHz millimeter waves can lead to heat stress and damage to the skin and trigger repair processes involving inflammation and tissue matrix restoration [27]. Two studies reporting the effects of neuroglia irradiation using 60 GHz low-power millimeter waves showed no alteration of stress gene expression of molecular chaperones such as clusterin and HSP70 and no effect of millimeter wave irradiation on endoplasmic reticulum stress-related gene expression and related protein secretion [28–29]. Six hours of continuous irradiation at 106 GHz increased spindle disruption during mitosis. However, no resulting chromosomal damage, such as DNA break or base instability sites, was reported [30–31]. Gapeyev et al. [32] found a protective effect against DNA damage caused by X-ray radiation by exposing mouse peripheral blood leukocytes to electromagnetic radiation at 42.2 GHz for 20 min in advance, which may be related to the adaptive response induced by reactive oxygen species. In general, in previous experimental studies, possible effects of millimeter wave irradiation on stress, repair, and other related gene expression have been identified. Still, there is no clear evidence of biogenetic damage caused by the non-thermal effects of millimeter waves.

3. Medical applications

3.1. Disease diagnosis and treatment

3.1.1. Oncology treatment

The examination of skin cancer often relies on the visual judgment of physicians, and experienced physicians can achieve greater than 80% accuracy. Confocal microscopy, as well as pathological examination, is required to confirm the diagnosis. Still, it is unsuitable for early screening of skin tumors due to the high price and invasive examination [33]. The millimeter wave detection method does not require tissue staining and is a non-invasive examination tool. Tumor and normal tissues have different dielectric properties due to their different tissue structure and vascularization, and generally, cancer cells have a higher water content [34]. This property provides the feasibility for millimeter wave detection. Mansutti et al. [35] designed a probe for early skin cancer detection and validated it on an artificial skin model, showing that the probe has a detection depth of 0.55 mm and can be used for skin detection in different body regions using the constructed algorithm. Mirbeik-Sabzevari et al. built a millimeter-wave imaging system with an ultrawide imaging bandwidth of 98 GHz obtained by synthesizing four subbands, which can provide ultra-high resolution of 200μm for early skin cancer detection. The researchers used the imaging system to image 21 non-melanoma skin cancer specimens. They compared them with histopathology, showing that the resulting high contrast three-dimensional images of the skin correctly showed the location of the cancerous tissue [36–37]. Subsequently, the team improved the millimeter wave detection device by reducing the number of antenna bands by 2, thus reducing detection time, and tested it in 136 in vivo skin cancer detections achieving a sensitivity and specificity of 97% and 98%, respectively [38]. Although the effectiveness for assisting in the early clinical determination of skin cancer needs further validation, present millimeter wave detection devices are promising for reducing unnecessary skin biopsies and providing a direction for further research on non-invasive early screening of skin cancer in the future. Furthermore, Summers et al. [39] investigated the use of millimeter waves in surgical margin evaluation of breast tumors using exploiting the dielectric properties of breast tissue (low-fat content of malignant tissue compared to normal breast tissue), and suggested a potential of millimeter waves in surgical margin evaluation applications, albeit with major limitations.

Several experimental studies have also been conducted to treat tumors. Beneduci et al. investigated the biological effects produced by low-power millimeter waves on a human melanoma cell line (RPMI7932) irradiated with different frequencies (51.05 GHz, 65.00 GHz, and 53.57–78.33 GHz wide-band frequency range), suggesting the antiproliferative effect of millimeter waves with the wide-band frequency range on tumor cells [40]. A murine experimental model of B16 F10 subcutaneous growth melanoma was used to assess the ability of millimeter wave treatment (61.22 GHz, 13.3×10^{-3} W/cm^2) to affect tumor growth. The results showed that nasal irradiation (15 min, 5 times/day) inhibited tumor growth. However, this inhibition was eliminated by blocking opioid receptors with naloxone, suggesting that opioid receptors may be involved in inhibition of tumor growth by millimeter waves [41]. Radzievsky et al. reported that millimeter waves might reduce cyclophosphamide-induced tumor metastasis by reducing NK cell inhibition by the chemotherapeutic drug cyclophosphamide, possibly associated with upregulation of NK cell functional activity by 42 GHz millimeter wave irradiation [24,42]. In vitro studies by Li et al. [43] suggested that millimeter wave radiation may induce apoptosis in human chondrosarcoma cells SW1353 by altering the ratio of the pro-apoptotic molecule Bax to the anti-apoptotic molecule Bcl-2. Recently, Zhao et al. [44] reported that exposure to 35.2 GHz millimeter waves promoted apoptosis in A375 human melanoma cells through the caspase-8 and caspase-3 pathways. These studies provide potential ideas for millimeter wave therapy for oncology treatment.

3.1.2. Pain management

A wide range of millimeter waves applications have been described to achieve relief of various pains, such as headaches, arthralgia, postoperative pain, and neuralgia. Sivachenko et al. used millimeter wave (40 GHz, 0.01 mW) irradiation of the cutaneous receptor area of the trigeminal nucleus in an experimental model of migraine in rats. The results showed that millimeter wave irradiation could exert a headache-reducing effect by suppressing the excitability of spinal trigeminal ganglion neurons [45]. In another study, researchers used millimeter wave therapy for pain management in patients with diffuse connective tissue disease (54–78 GHz, 2.5 mW/cm^2) with an exposure time of (35 ± 5) min. Eleven of the 12 patients achieved a reduction in the need for analgesics after receiving millimeter wave therapy [46]. Similarly, Usichenko reported that millimeter-wave therapy reduced the need for pain medication in patients after knee arthroplasty [47]. Radzievsky et al. conducted a double-blind, randomized, crossover, prospective trial demonstrating that millimeter wave therapy can reduce pain sensitivity. The team followed up by using opioid receptor selective blockers to reduce the pain-relieving effects of millimeter waves and using enzyme linked immunosorbent assay (ELISA) to detect endogenous opioid receptor agonists in the central nervous system, suggesting that millimeter wave therapy may relieve pain by affecting endogenous opioid receptor agonists [48–49].

3.1.3. Other diseases

Usichenko et al. [50] applied millimeter wave therapy to the supplementary treatment of rheumatoid arthritis. They showed that patients in the millimeter wave treatment group achieved improvements in pain and joint stiffness compared to the control group. A set of experimental studies found that millimeter wave treatment inhibited chondrocyte apoptosis by suppressing (Ca^{2+}), inhibiting calpain activation, which initiates apoptosis, and increased aggregated expression of collagen II and chondrocytes. Millimeter waves inhibit the mitochondria-dependent pathway of apoptosis in chondrocytes as well as single nucleotide polymorphism (SNP)-induced chondrocyte apoptosis via the p38MAPK pathway [51–53]. Wu et al. [54] reported that millimeter wave treatment successfully induced the differentiation of mesenchymal stem cells (MSCs) into chondrocytes and the degree of differentiation increased with increasing treatment time. These studies may partially explain their clinical effectiveness in the treatment of osteoarthritis. One study reported that millimeter wave therapy applied to the treatment of acute pancreatitis reduced the systemic inflammatory response and improved the general condition of patients but had no significant effect on the length of hospital stay and confirmed the microcirculatory response of millimeter wave in normalizing capillary blood flow in the early treatment of pancreatitis [55–56]. Smulders et al. [57] showed that millimeter waves could promote wound healing and accelerate repair mechanisms. In addition, Radzievsky et al. [58] used a millimeter wave (61.22 GHz, 15 mW/cm^2) to irradiate the nose of mice for 15 min/d and showed that millimeter wave could alter the transit function of the small intestine or colon of mice. Millimeter waves have also been used to treat physical injuries due to sports or other causes. Millimeter waves have been shown to achieve benefits in treating soft tissue injuries and fractures, reducing edema, accelerating wound healing, and reducing pain. The therapeutic effects of the injury may be based on the affinity for water-containing tissues, which can improve the metabolism and blood circulation of local tissues, accelerate the absorption of tissue edema, and accelerate the excretion of pathological products and absorption of metabolites, thus achieving the therapeutic purposes of anti-inflammation, decongestion, and pain relief [59].

3.2. Monitoring vital signs

Respiration, heartbeat, pulse, and blood pressure are important vital signs for humans, which not only reflect the health status of the human body but also provide an important reference basis for the treatment of diseases. Current vital sign detection devices mainly include electrocardiogram (ECG) monitors, medical sleep detectors, electronic blood pressure monitors, and wearable devices [60]. Contact detection devices, such as medical ECG monitors, measure electrophysiological activity and have high measurement accuracy, better real-time detection, and stability; however, they still present problems such as large size, cost, and are inconvenient to use. Furthermore, these devices may cause additional damage to some patients, such as those with large burns. At the same time, in the case of daily home-based monitoring, the prolonged use of such equipment attached to the skin can easily cause skin damage and affect the quality of daily activity and sleep. As a non-contact sensor, millimeter wave-based monitoring radar can extract human vital sign information using micro-motion signals from the human body surface and can continuously and non-invasively collect human vital signs and activity information [61]. Lv et al. [62] designed a respiration and heart rate monitoring system using 120 GHz band millimeter wave radar for experimental use. The detection of human respiration and heart rate at a distance of 1 m could achieve an accuracy of more than 90%. The detection algorithm designed by Wang et al. [63] based on 77 GHz millimeter wave radar reached a 93% accuracy in respiration and heart rate detection compared to contact detection results as a standard. Johnson et al. [64] proposed a millimeter wave radar system for contactless pulse measurement and measured significant pulse waves from the radial artery, offering the possibility of millimeter wave radar for pulse waveform analysis and monitoring of blood pressure. These monitoring devices can continuously produce vital signs data through machine learning analysis, achieve sleep health analysis, disease-assisted diagnosis and treatment, predict or detect abnormalities or disease states in advance, and improve medical efficiency. In terms of human activity monitoring, wearable devices are affected by range and usage habits of older adults, making it difficult for them be effective at all times. Monitoring equipment based on cameras or thermal infrared cameras [65], in situations of poor light, clothing cover, and temperature changes, have shown that the efficacy is not satisfactory. At the same time, camera use also presents issues concerning privacy protection because falls often occur in the bathroom and other places demanding a high degree of privacy. Millimeter wave radar is gaining attention because of its advantages including privacy protection. Alanazi et al. [66] developed a multilayer convolutional neural network to identify and classify five different gait patterns using millimeter wave radar data and could obtain an accuracy of 95.7% to 98.8%. A skeletal key point estimator is reported using millimeter wave radar data, measuring 25 skeletal key points and providing an error margin of <3 cm [67]. These studies suggest that millimeter wave radar could provide the ability to remotely monitor patients for medical rehabilitation applications, without the need for users to wear wearable devices that interfere with their daily activities. It can also detect events such as falls to avoid serious consequences due to an untimely rescue [68].

4. Summary

Evidence supports the potential benefits of millimeter wave therapy based on extensive studies in animal models and in clinical trials that have demonstrated a wide range of biological effects of millimeter wave therapy. Millimeter wave therapy can be used clinically for simple physical therapy and supplementary treatment of various diseases such as cancer, pain management, tissue damage repair, and digestive system diseases. In the millimeter wave radar-based vital signs monitoring field, IoT-based sign detection and monitoring are developing in the direction of greater safety and intelligence, and non-contact vital signs detection and monitoring will represent a future development trend. The development of millimeter wave bio-radar technology provides technical support for achieving such prospects. However, the mechanisms underlying millimeter wave activity have not yet been firmly established, and the theoretical basis of its specific application parameters, biological effects, and molecular cytological mechanisms are still not well clarified. In practice, selecting the optimal time, power density, and radiation site for millimeter wave radiation therapy is more complicated for different diseases and their different stages of development. The lack of evidence-based medical evidence requires further in-depth study. At the same time, clinical epidemiological surveys and hygienic studies on millimeter wave radiation should receive greater attention. The safety of the prolonged use of millimeter wave deserves further study, and millimeter wave radiation health protection standards need to be established. This review also has some limitations as the sample size of the reported studies is perhaps not sufficiently large enough to allow a comprehensive overview of medical applications of millimeter waves. We hope that this study may act as a reference for future researchers in related fields.

Conflicts of interest statement

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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Author contributions

Honglin Wang, Lin Lu, and Pengran Liu completed the research and wrote the article; Jiayao Zhang, Songxiang Liu, Tongtong Huo, Yi Xie, Hong Zhou, Mingdi Xue, Ying Fang, and Jiaming Yang made the previous investigation and survey, and also revised the article; Zhewei Ye designed and guided the research.

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