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Prominence of Curcumin in Anticancer Strategies and İnnovation in Bioimaging.

Antikanser Stratejilerinde Kurkuminin Önemi ve Biyolojik Görüntülemede Yenilik

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ABSTRACT

Curcumin (CUR), a natural polyphenol derived from the rhizomes of Curcuma longa (turmeric), has garnered significant attention in recent years for its multifaceted potential in anticancer therapy and bio-imaging applications. This review article comprehensively explores the diverse anticancer properties of CUR, encompassing its potent anti-inflammatory, antioxidant, and anti-proliferative effects, as well as its ability to induce apoptosis and inhibit angiogenesis, making it a promising candidate in the fight against cancer. In addition to its therapeutic potential, CUR's unique physicochemical properties have enabled its utility as a versatile imaging agent for various bio-imaging modalities, including fluorescence imaging, magnetic resonance imaging (MRI), and positron emission tomography (PET). We investigate the molecular mechanisms underlying CUR's bio-imaging capabilities and discuss its various applications in cancer diagnosis, monitoring treatment responses, and elucidating biological processes. This comprehensive review provides valuable insights into the dual role of CUR as an anticancer agent and a bio-imaging tool, elucidate its potential in the development of novel cancer therapies and diagnostic approaches. The amalgamation of CUR's bio-imaging and therapeutic properties suggests its future as a pivotal player in personalized medicine and precision oncology.

Key Words
Curcumin, bio-imaging, anticancer;

ÖZ

Curcumin (CUR), zencefil kökü (zerdeçal) Curcuma longa'dan türetilen doğal bir polifenoldür ve son yıllarda kanser tedavisi ve biyogörüntüleme uygulamalarındaki çok yönlü potansiyeli nedeniyle önemli ilgi görmüştür. Bu derleme makalesi, CUR'un çeşitli kanser karşıtı özelliklerini kapsamlı bir şekilde ele almaktadır; güçlü anti-inflamatuar, antioksidan ve anti-proliferatif etkilerini, apoptozu indükleme yeteneğini ve anjiyogenezin inhibisyonunu içermektedir, bu da onu kanserle mücadelede umut vaat eden bir aday haline getirmektedir. CUR'un terapötik potansiyeline ek olarak, CUR'un benzersiz fizikokimyasal özellikleri, floresans görüntüleme, manyetik rezonans görüntüleme (MRI) ve pozitron emisyon tomografisi (PET) gibi çeşitli biyogörüntüleme yöntemleri için çok yönlü bir görüntüleme ajanı olarak kullanılmasını sağlamıştır. CUR'un biyogörüntüleme yeteneklerinin moleküler mekanizmalarını araştırıyor ve kanser teşhisi, tedavi yanıtının izlenmesi ve biyolojik süreçlerin aydınlatılması gibi çeşitli alanlardaki uygulamalarını tartışıyoruz. Bu kapsamlı derleme, CUR'un hem bir anti kanser ajanı hem de bir biyogörüntüleme aracı olarak çift rolünün değerli içgörüler sağlar ve yeni kanser tedavileri ve tanı yaklaşımlarının geliştirilmesindeki potansiyelini açıklar. CUR'un biyogörüntüleme ve terapötik özelliklerinin birleştirilmesi, kişiselleştirilmiş tıp ve hassas onkolojide kilit bir rol oynaması gerektiğini öne sürmektedir.

Anahtar Kelimeler
Curcumin; biyo-görüntüleme, antikanser.

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INTRODUCTION

The dried and ground rhizome of Curcuma longa Linn has a rich history of use in Asian medicine dating back to the 2nd millennium BC [1] Interest in phytochemicals like CUR derived from turmeric continues to grow. While the chemical structure of CUR was known as far back as 1913 [2], its biological properties were not extensively studied and reported until the 1970s [1,3]. Additionally, its systematic fluorescent properties were not discovered and reported until 1985 [4]. CURoids, including CUR (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), commonly referred to as diferuloylmethane, have received "Generally Recognized as Safe" (GRAS) status from the US Food and Drug Administration (FDA) [5-7]. Turmeric, or Curcuma longa, typically contains around 2-8% CUR by weight. CUR, along with certain analogs, contributes to the bright yellow color of turmeric [8]. Research into the potential anticancer properties of CUR gained momentum in the 1990s, particularly after its ability to suppress the activation of the transcription factor nuclear factor kappa-B (NF-κB) was recognized [9]. Commercially available CUR products typically consist of not only CUR (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) but also three other curcuminoids, namely, approximately 17% dimethoxy curcumin, 3% bisdemethoxy curcumin, with the majority being CUR itself. CUR displays tautomerism within its molecular structure. In non-polar solvents, it predominantly assumes the enol form, facilitated by intramolecular hydrogen bond formation. However, in polar solvents, CUR adopts the diketo form. The keto form of CUR functions as a proton donor in acidic and neutral environments, while at pH levels exceeding 8.0, the enol form takes precedence, serving as an electron donor. CUR's possession of phenolic, b-diketone, and methoxy groups contributes to its proficiency in scavenging free radicals. This attribute is among the factors underlying its anticancer properties [10]. CUR's antibacterial activity was initially showcased in Nature back in 1949 [11], and since then, it has been extensively examined against various gram-negative and gram-positive bacteria. The antimicrobial characteristics of CUR have been the subject of extensive research [12-17]. Antioxidant therapies can be realized by integrating antioxidant agents into wound dressings, enabling them to specifically target and counteract Reactive Oxygen Species (ROS) at the wound site. This strategy is deemed essential for improving the recovery of chronic wounds since the elimination of ROS is a pivotal approach. The generation of various ROS, encompassing hydroxyl radicals, superoxide radicals, nitrogen dioxide radicals, and lipid peroxyl radicals, is intimately associated with the onset of oxidative stress. Recent animal studies have underscored the noteworthy contribution of CUR in defending against oxidative stress by efficiently scavenging these highly reactive free radicals, consequently facilitating the healing process [18-21]. The presence of phenolic hydroxyl groups in CUR is instrumental in its ability to scavenge ROS, while its diketone structure plays a role in binding to metals. Another key aspect of CUR's antioxidant activity is its ability to activate cytoprotective signaling components through the nuclear factor erythroid 2-associated factor (Nrf2). This molecular mechanism is closely associated with the antioxidant properties of CUR and contributes to its ability to combat oxidative stress [22]. These effects include the upregulation of pro-apoptotic proteins like Bax and p53, the suppression of factors involved in angiogenesis such as vascular endothelial growth factor (VEGF) and hypoxia-induced factor 1-alpha (HIF-1), as well as the reduction of inflammatory responses.

CUR also induces autophagy and has been associated with overcoming drug resistance in cancer cells. These multifaceted actions contribute to its effectiveness in combating cancer [23-25]. CUR also serves as a potent anti-inflammatory and antiviral agent [26,27]. Notably, it has been observed to reduce opioid tolerance [28]. Its pharmacological potential is extensive, encompassing anti-inflammatory, antioxidant, anti-proliferative, chemo-sensitizing, and cell cycle arrest properties.

Moreover, CUR has demonstrated apoptotic effects against various cancer cell types, including colorectal, breast, pancreatic, and colon cancers. These diverse properties highlight its significance in both treatment and prevention [29]. CUR has demonstrated antiviral efficacy against a multitude of viruses, encompassing influenza viruses, hepatitis viruses, chikungunya virus (CHIKV), and emerging arboviruses like the Zika virus (ZIKV). Importantly, CUR has proven effective in mitigating the transmission of sexually transmitted diseases, including human immunodeficiency virus (HIV), human papillomavirus (HPV), and herpes simplex virus 2 (HSV-2). These findings underscore its substantial potential in combating a diverse array of viral infections. [30,31].

Anticancer properties

The therapeutic potential of CUR has prompted researchers to explore its combination with other drugs. Research has provided evidence that the combination of CUR with doxorubicin and cisplatin yields additive and synergistic cytotoxic effects on hepatic cancer cells. This implies that CUR has the potential to enhance the efficacy of conventional chemotherapy drugs when administered together, which could lead to improved cancer treatment outcomes [32]. In a correlated investigation, the combination of CUR with gemcitabine significantly decreased the expression of the cell proliferation marker Ki-67 in the tumor tissues of mice. This observation suggests that CUR has a chemo-sensitizing effect when used in conjunction with gemcitabine, potentially enhancing the efficacy of the chemotherapy [33]. In another in vivo study involving mice with multidrug-resistant ovarian tumors, the mice were subjected to a 4-week treatment regimen. This treatment included docetaxel in combination with free-form CUR. The results indicated that both CUR alone and in combination with docetaxel led to significant reductions in tumor growth, with reductions of 47% and 58%, respectively. This suggests that CUR may enhance the therapeutic efficacy of docetaxel in multidrug-resistant ovarian tumors [34]. In a study investigating the pharmacokinetics and biodistribution of a CUR nanosuspension, which consisted of 210 nm TPGS (d-α-tocopheryl polyethylene glycol 1000 succinate), following intravenous doses of 15 mg/kg in rabbits and 20 mg/kg in mice, notable findings were observed. The AUC (area under the curve) for the CUR nanosuspension was reported to be 700 µg/ml, with a mean residence time of 194 minutes. In contrast, when CUR was administered in a dimethylacetamide and PEG 400 diluted isotonic dextrose solution, the AUC was reported as 145 µg/ml, with a mean residence time of 16 minutes. This suggests that AUC and mean residence time were approximately 4-fold and 11-fold higher after nanoencapsulation, respectively. Furthermore, it was observed that 10 minutes after injection, CUR nanosuspensions displayed remarkable accumulation in the lungs, resulting in notably higher concentrations, reaching 10 µg per gram of organ tissue. Elevated concentrations were also observed in the spleen (8 µg/g) and liver (6 µg/g). In contrast, following the administration of CUR released from its formulation, the highest concentrations were detected in the lung (0.5 µg/g), with relatively minimal levels in the liver and spleen, measuring around 0.1 µg/g. The researchers proposed that CUR nanosuspensions were taken up by macrophages of the reticuloendothelial system situated in the spleen and lung. Within these phagocytic cells, nanoparticles can dissolve, resulting in a gradual release of CUR into the bloodstream [35,36]. CUR is known to be highly susceptible to conjugation, particularly through processes like glucuronidation and sulfation, especially in humans. These conjugation reactions can lead to reduced CUR availability at the systemic level. It's important to note that the uptake of CUR can vary among different cell types, depending on the polarity and hydrophobicity of the compounds within the cells. To address the challenge of low bioavailability of poorly absorbed drugs in the bloodstream, various strategies have been explored. One such strategy involves formulating CUR with phosphatidylcholine. This formulation has been shown to enhance the absorption of CUR, resulting in improved bioavailability. This approach may help overcome some of the limitations associated with CUR's poor absorption and conjugation in the body [37]. It is worth noting that CUR possesses the capability to influence multiple cell signaling pathways, exerting adverse effects on cancer cells. CUR has demonstrated favorable outcomes in both in vivo and in vitro [38] models. It exhibits concentration-dependent anti-proliferative potential and complements anticancer agents effectively, reducing the survival of prostate cancer cells, for instance. CUR also impacts cancer stem cells, exhibits anti-metastatic properties, and is well-tolerated at doses nearing 8000 mg/day [39-41]. Additionally, a study suggests that CUR can impede the progression of hepatoma cells and metastasis induced by epithelial-mesenchymal transition (EMT) through the modulation of Transforming Growth Factor TGF-ß1 [42]. Another investigation examining the impact of orally administered CUR on colon tumor apoptosis indicates that CUR, as a dietary supplement, may enhance apoptosis and impede tumor advancement [43]. Furthermore, analogous results have been observed in various cell lines derived from malignant tumors, including those associated with breast, oral epithelium, kidney, melanoma, hepatocellular, lymphoid, myeloid, and prostate cancers. [44]. When exposed to a 9 µM CUR treatment in vitro, mouse sarcoma, HT29 human colon carcinoma, mouse embryo fibroblast, , human kidney carcinoma, and human hepatocellular carcinoma cell lines displayed secondary cell shrinkage, chromatin condensation, and DNA fragmentation [45]. Studies conducted ex vivo have indicated that the ability to induce macrophage NOS activity is hindered by CUR concentrations ranging from 1 to 20 µM [46]. The prognosis of lung and other cancers is

linked to the expression of angiogenic growth factors. In vivo experiments using a mouse corneal model have shown that CUR at concentrations of ≥10 μM can effectively inhibit angiogenesis [47]. CUR also impacts the production of angiogenic growth factors, a crucial aspect of new vessel formation, in both non-malignant and malignant cells [48].

Bio-imaging by CUR

In recent years, a shift has occurred in the use of organic dye probes. Instead of employing single organic dyes, these dyes are now encapsulated within particle matrices. This approach offers several advantages: the resulting particles are significantly brighter than single dyes, more photostable, and the encapsulation enhances their stability and biocompatibility. However, this doesn't apply universally to all particles. Quantum Dot nanoparticles, on the other hand, are intrinsically fluorescent and possess outstanding optical properties. Furthermore, the covalent triple dye labeling method can be extended to a variety of energy transfer dyes, enabling the creation of a broad library of FRET NP barcodes. This opens the door to multiplexing technologies that can harness the advantages of NPs and microfluidics. Additionally, non-invasive molecular imaging technologies can be developed using FRET NPs, thanks to their large Stokes shift, which facilitates detection in samples with significant light scattering or the presence of endogenous fluorescent compounds [49].

The fluorescent characteristics of CUR have recently captured the interest of researchers, alongside its therapeutic properties. CUR is commonly utilized as a food coloring agent because of its pronounced absorption and visible-region fluorescence emission, particularly in its monomeric state. The photoluminescent behavior of CUR is influenced by various factors, including solvent polarity, pH, and concentration. In polar solvents like water, CUR displays subdued photoluminescence with its maximum emission peak at approximately 550 nm. However, in non-polar solvents like ethanol, CUR's photoluminescent properties are enhanced, and the maximum emission peak shifts to around 430 nm. The pH of the solvent also impacts CUR's photoluminescent characteristics, with higher pH levels leading to a decrease in fluorescence intensity. CUR exhibits strong absorption in acidic or neutral aqueous solutions, with a maximum wavelength (λmax) ranging from 410 to 430 nm. It displays weak absorption between 260 and 280 nm due to $\pi \rightarrow \pi^*$ transitions, and there's also a slight n to π^* transition near 375 nm [50,51]. CUR and its derivatives exhibit excellent electrical and optical properties due to their highly symmetrical delocalized π electrons. What sets CUR apart is its ability to interact with a wide range of molecular targets while having fewer side effects on the human body. By modifying the π-conjugate system and ß-diketone structure, it's possible to enhance the fluorescence emission wavelength and intensity of CUR. Researchers are leveraging these properties to develop CUR-based fluorescent probes that bind with various target molecules. This allows for the analysis of factors influencing the fluorescence intensity and emission wavelength of these probes, ultimately leading to the creation of CUR probes with higher sensitivity and selectivity. Such an approach holds significant promise for applications in in vivo fluorescent imaging [52]. CUR has the ability to enhance a variety of biochemical processes by contributing hydrogen atoms, thereby inducing oxidation, both irreversible and reversible nucleophilic reactions (such as the Michael reaction), hydrolysis, and enzymatic reactions [53].

The photochemical properties of CUR are greatly influenced by the solvent in which it is placed. In biological contexts, the photodegradation of CUR can lead to the formation of products like superoxide and singlet oxygen, which have been linked to the phototoxic effects of CUR within the cellular environment [54]. Thus, the fluorescence of CUR exhibits a broad band in various solvents: in acetonitrile with a maximum wavelength (λmax) of 524 nm, in ethanol with λmax at 549 nm, and in micellar solutions with λmax at 557 nm. However, it shows different fluorescence patterns in toluene, with peaks at λmax of 460 and 488 nm. Furthermore the fluorescence quantum yield of CUR is low in sodium dodecyl sulfate solution (ϕ= 0.011) but higher in acetonitrile (ϕ= 0.104). Additionally, the production of singlet oxygen by CUR is approximately 10 times lower in alcohols, and singlet oxygen phosphorescence is not observed in sodium dodecyl sulfate micelles. These variations in fluorescence and singlet oxygen production highlight the sensitivity of CUR's photophysical properties to its environment [55]. Traditional organic fluorescent dyes and probes, including carboxytetramethylrhodamine, fluorescent 5-carboxyfluorescein, cyanine, fluorescein isothiocyanate, and rhodamine, have been extensively employed in bioimaging applications [56]. However, these dyes come with certain drawbacks that can limit their utility in bioimaging, such as low fluorescence intensity, poor photostability, and limited stability. On the

other hand, numerous studies in the field of bioimaging and protein detection have highlighted the promising potential of CUR-based fluorescent probes. These probes offer exciting prospects for in vivo applications, extending beyond merely identifying drugs themselves. They can address some of the limitations associated with traditional fluorescent dyes, making them a valuable tool in the field of bioimaging [57,58]. CUR's versatility extends to its use in positron emission computed tomography (PET) imaging studies when labeled with the radioactive isotope fluoro-18 [59]. However, PET scanning has certain drawbacks, such as high detection costs, time-consuming procedures, and radiation hazards, which have limited its clinical application. Recent advancements have seen the adoption of near-infrared fluorescent (NIRF) probes for in vivo imaging. NIRF probes offer several advantages, including non-invasiveness, safety, cost-effectiveness, rapid imaging, deep tissue penetration, and minimal interference from native luminescence within living tissues. Numerous cyanine dyes and their derivatives, including commercially accessible NIRF probes, are available; however, their considerable molecular dimensions and electrical charges can impede their capacity to breach the blood-brain barrier (BBB), thereby diminishing their suitability for tagging intracranial Aß plaques. Conversely, fluorescent imaging has effectively showcased the labeling of CUR using diverse anti-Aß monoclonal antibodies (mAbs), facilitating the detection of intracellular and extracellular deposits across retinal layers in Alzheimer's disease (AD) patients. This methodology holds great potential in the realm of AD research and diagnosis [60].

Gholibegloo et al. introduced a novel theranostic system in their study. They created this system by combining cyclodextrin nanosponge polymer with magnetite nanoparticles (Fe_3O_4/CDNS NPs) and then adding folic acid (FA) as a targeting agent (Fe_3O_4/CDNS-FA). The hydrophobic model drug, CUR, was loaded into the CDNS cavity and polymeric matrix to create Fe_3O_4/CDNS-FA@CUR NPs. The study further investigated blood compatibility and found minor hemolytic activity. In vitro MRI studies indicated a negative signal increase in cells, indicating the nanocarrier's potential for diagnostic purposes. The T_2 MR signal intensity was notably higher in M109 cells compared to MCF 10A cells, suggesting selective cellular uptake of the Fe_3O_4/CDNS-FA@CUR NPs by cancer cells. Additionally, it can serve as a negative contrast agent for MRI due to its magnetic properties and selective targeting capabilities [61]. In their study, Qin et al. developed Zn(II) complex-based fluorescent probes using cryptolepine–CUR derivatives, specifically [Zn(BQ)Cl_2] (BQ-Zn) and [Zn(BQ)(Cur)]Cl (BQCur-Zn), for the purpose of simple and label-free fluorescent detection of apoptosis, a significant biological process. These probes were found to have the ability to enhance mitochondrion-mediated apoptosis and improve the therapeutic effects on tumors, both in vitro and in vivo. The researchers designed two new red fluorescent probes based on Zn(II) complexes, incorporating cryptolepine-H-cur derivatives with a focus on mitochondrial membrane targeting. When exposed to visible light, BQCur-Zn was shown to effectively strengthen mitochondrion-mediated apoptosis and enhance the therapeutic outcomes for tumors, especially during photodynamic therapy (PDT) [62]. Liu et al. developed 2D nanosheets with an exceptionally high 59.6% CUR loading and strong water stability using a unique nanoparticles-induced assemble strategy. They coated these nanosheets with polydopamine, enabling photothermal effects and multimodal imaging. This approach allowed for precise and efficient tumor ablation, particularly when combined with CUR-based chemotherapy. In vivo experiments confirmed their effectiveness in guiding potent combined tumor treatment while causing minimal side effects on normal tissues. This novel strategy offers a promising avenue for designing drug-loaded nanomedicine with high drug content and well-defined shapes for cancer theranostics [63]. Singh et al. introduced an innovative polymeric prodrug named poly(oxalate-co-CUR) (POC), in which CUR is integrated into a polyoxalate backbone responsive to H_2O_2. These POC particles effectively scavenge H_2O_2 and release CUR in reaction to H_2O_2 levels. Experimental results revealed that POC particles exhibited remarkable antioxidant and anti-inflammatory properties in activated cells. When administered intravenously to mice intoxicated with acetaminophen, they notably mitigated liver damage and apoptotic cell death. An intriguing aspect is that POC particles also enhanced ultrasound contrast within the intoxicated liver by generating CO_2 bubbles via the H_2O_2-triggered oxidation of peroxalate esters. With their responsiveness to H_2O_2 and robust antioxidant capabilities, POC particles offer significant potential as theranostic agents for diseases associated with elevated H_2O_2 levels [64].

Hu et al. modified CUR to create polarity-specific fluorescent probes, 0301 and 0302. These probes change color in response to changes in environmental polarity and allow for clear imaging of lysosomal polarity in cells.

Probe 0301 distinguishes between cancer and normal cells, making it a valuable tool for studying biological processes related to polarity. These probes are highly sensitive to polarity and maintain stability against various interferences, offering promising applications in Researchs [65].

Yan et al. utilized carbon dots (CDs) as a ratiometric probe for detecting CUR and Fe^{3+}. They observed fluorescence quenching at 420 nm due to the inner filter effect (IFE) and fluorescence enhancement at 525 nm upon the addition of CUR. The system demonstrated a linear response to CUR concentrations in the range of 5–30 µM, with a limit of detection of 21.79 nM. Upon introducing Fe^{3+} into the CDs-CUR system, CUR complexed with Fe^{3+}, causing quenching of CUR fluorescence at 525 nm. This reduced spectral overlap between CUR and CDs, inhibiting the IFE and leading to the recovery of CD fluorescence at 420 nm. The system exhibited a linear response to Fe^{3+} concentrations in the range of 2–14 µM, with a limit of detection of 18.11 nM. The CDs-CUR system was successfully applied for H1299 cell imaging and holds potential for fluorescent labeling and tumor cell inhibition. Furthermore, it was employed to study PVDF membrane fouling by iron flocculants in wastewater treatment [66]. In another study, Çıkrık et al. developed curcumin-imprinted and non-imprinted poly(2-hydroxyethyl methacrylate-N-methacryloyl-L-tryptophan) (poly(HEMA-MATrp)) nanoparticle-based surface plasmon resonance (SPR) nanosensors for curcumin detection. These nanosensors were characterized using zeta-size analysis, Fourier transform infrared spectroscopy, and scanning electron microscopy. The nanoparticles were then attached to SPR chips and further characterized with atomic force microscopy, ellipsometry, and contact angle measurements. Kinetic studies on curcumin in aqueous solutions (0.01–150 mg/L) showed a response time of 14 minutes for equilibration, adsorption, and desorption cycles. The curcumin-imprinted SPR nanosensors had detection and quantification limits of 0.0012 mg/L and 0.0040 mg/L, respectively, and their performance was validated with liquid chromatography-tandem mass spectrometry (LC-MS) [67]. Ferreira et al. ingeniously designed a family of CUR-based molecular probes with tunable emission colors, derived from boron diketonate complexes. Leveraging CUR's fluorescence and its moderate toxicity to fungi, they developed probes that could enter fungal cells without causing noticeable harm, precisely localizing within sub-cellular organelles for visualization. These versatile probes not only offered a spectrum of emission colors from blue to red but also exhibited a high degree of selectivity for sub-cellular compartments. This innovation overcame the limitations of traditional fungal dyes, which typically provide only a single staining color, making these CUR-based probes ideal for co-staining experiments and advancing fungal cell visualization techniques [68]. Shao et al. addressed the solubility and biocompatibility challenges associated with CUR by preparing various CUR fluorescent complexes, including EPO-CUR (EPO-Cur), L100-55-CUR (L100-55-Cur), EPO-CUR-β-cyclodextrin (EPO-Cur-β-cd), and L100-55-CUR-β-cyclodextrin (L100-55-Cur-β-cd). These complexes exhibited significantly enhanced fluorescence emission intensities, reaching hundreds of times that of CUR alone when dissolved in polar solvents. To assess their compatibility with tumor cells directly, live cell fluorescence imaging was conducted, revealing excellent biocompatibility for all four CUR fluorescent complexes. Notably, the complexes EPO-Cur-β-cd and L100-55-Cur-β-cd outperformed EPO-Cur and L100-55-Cur in terms of their effectiveness [69]. Yaqian et al. synthesized bis-iodine-labeled CUR (BICUR) and evaluated its performance through in vivo and in vitro experiments. In vitro binding assays showed that BICUR had Kd values of 46.29 nM and 64.29 nM with Aβ1-40 and Aβ1-42 aggregates, respectively. BICUR effectively stained Aβ plaques in Alzheimer's disease brain sections, similar to other CUR derivatives. The compound exhibited favorable properties, with a Log P value of 1.45, high brain uptake, rapid clearance, and low toxicity, with an LD50 greater than 100 mg/kg in acute toxicity testing. BICUR also demonstrated excellent stability in vitro, with 86.68% remaining unchanged after 120 minutes of incubation in mouse brain homogenate. Additionally, BICUR enhanced CT imaging, making it a potential targeted imaging agent for detecting Aβ plaques in the brain with high sensitivity and differentiation from surrounding tissues [70]. Wang et al. ingeniously altered the luminescent properties of CUR (Cur) from being "off" to becoming "on" by encapsulating it within poly (D, L-lactide-co-glycolide) acid (PLGA) nanoparticles embedded in a polyvinyl alcohol (PVA) emulsifier, giving rise to Cur@PLGA-NPs. To identify the most efficient carriers for Cur luminescence, they explored various nanoformulations, including liposomes and bovine serum albumin (BSA) nanoparticles. Among these, Cur@PLGA-NPs exhibited the most pronounced fluorescence intensity, primarily attributed to aggregation-induced emission (AIE), boasting quantum yields of 23.78% in aqueous

solution and 21.52% in the solid state. Leveraging the robust AIE-based fluorescence, Cur@PLGA-NPs served as nano-AIE probes for cell bioimaging, leading to the observation of vivid red fluorescent signals in CT26 cells post-treatment. These findings introduce a groundbreaking amorphous AIE formulation with imaging and bioactive capabilities, underscoring the potential of Cur@PLGA-NPs as a promising tool for cell imaging and clinical applications [71]. Gangemi et al. designed a novel bioimaging system consisting of CUR and BODIPY subunits, enabling efficient energy transfer for far-red emissions suitable for microscopy. They encapsulated this system within biocompatible MCM-41 nanoparticles, preserving its brightness and allowing it to target the cell nucleus. This newly developed CB-Green system offers an ideal bioimaging tool with a large Stokes shift, long emission wavelengths, and specific intracellular staining capabilities. Its encapsulation strategy within silica nanoparticles ensures bright and efficient energy transfer, making it a promising candidate for bioimaging applications [72].

Yadav et al. synthesized carbon quantum dots (CQDs) using an eco-friendly reflux method and explored their potential as carriers for the antitumor drug CUR. They investigated drug loading and release mechanisms in vitro and assessed the in vivo bioimaging capabilities of CQDs. They employed FRET with CQDs as donors and CUR as acceptors to examine drug loading heterogeneity in live *Escherichia coli* cells. Their study highlights the versatile application of CQDs in bioimaging and FRET techniques, demonstrating their biocompatibility and potential for targeted CUR delivery within live cells [73]. Su et al. synthesized CUR carbon quantum dots (Cur-NRCQDs) with combined antibacterial and imaging properties. Cur-NRCQDs enhanced the photosensitizing efficiency of Cur, exhibited good stability, and improved reactive oxygen species (ROS) generation, boosting antibacterial activity. Under xenon lamp irradiation, Cur-NRCQDs effectively inactivated *Staphylococcus aureus* and *Escherichia coli* by disrupting cell membranes through ROS production. These nanoparticles demonstrated excellent biocompatibility, allowing them to enter bacteria and cells for imaging purposes. Cur-NRCQDs hold promise for antibacterial photodynamic therapy (aPDT) and fluorescent bioimaging, making them ideal for both treatment and diagnosis applications in bacteria and cell tissues [74].

Zhu et al. developed a fluorescent probe, DFB-1, based on CURoid difluoroboron. DFB-1 contains a triphenylphosphine (TPP) unit for mitochondrial targeting and aryl boronates as an H_2O_2-sensitive group. This dual-channel probe offers several key features: (i) it responds to H_2O_2 with a large shift in fluorescence; (ii) it actively targets mitochondria; (iii) it emits near-infrared (NIR) fluorescence with a high signal-to-background ratio. DFB-1 effectively detects endogenous H_2O_2 with an impressive low detection limit of 0.025 μM and can distinguish H_2O_2 variations between hepatocellular carcinoma and colorectal cancer cells. This versatile probe provides a valuable tool for studying the role of H_2O_2 in biological processes and offers new possibilities for in vivo imaging to monitor changes in protein activity and intracellular events [75]. Tannus et al. developed a straightforward method to convert an emissive CUR framework into a novel chemiluminescent luminophore. They created a bromo-CUR intermediate for a Stille cross-coupling reaction with a unique adamantyl stannane reagent. This process allowed them to produce a CUR enolether precursor, which could be oxidized with singlet oxygen to generate a CUR chemiluminescent luminophore. This new luminophore emitted intense light with a spectrum closely related to its CUR benzoate structure. This innovative approach represents the first instance of a chemiluminescent luminophore built upon the emissive properties of the CUR molecular structure. The authors anticipate that this method could be valuable for developing new chemiluminescent luminophores by converting other known emissive dyes into dioxetane precursors through the Stille cross-coupling technique [76].

Li et al. developed two photosensitizers, CCOH and CCN, by incorporating coumarin into the CUR (CUR) structure. These novel photosensitizers outperformed CUR by generating more ROS synergistically through type I and type II pathways upon light exposure. In cell experiments, CCN exhibited excellent LD-targeting capabilities and could be used to monitor changes in LD morphology and quantity in tumor cells during PDT. Both light-only and CCN-only groups showed strong green fluorescence, demonstrating CCN's biocompatibility. In the CCN irradiation group, nearly all tumor cells were eliminated, while under hypoxic conditions, some cells succumbed, aligning with MTT assay results. These findings suggest that CCN holds potential for use in hypoxia PDT guided by LD imaging due to its biocompatibility and high phototoxicity [77].

Conclusion

In conclusion, the remarkable natural compound CUR has emerged as a pivotal player in the realms of anticancer therapy and bio-imaging. Its multifaceted attributes, including anti-inflammatory, antioxidant, and anti-proliferative effects, hold immense promise in the battle against cancer. Furthermore, CUR's ability to induce apoptosis, inhibit angiogenesis, and interfere with various signaling pathways places it at the forefront of innovative cancer treatment strategies. The evidence presented in this review underscores the therapeutic potential of CUR in addressing the complex challenges of cancer, making it a compelling subject of further investigation and clinical development. Beyond its therapeutic applications, CUR's unique physicochemical properties render it a versatile bio-imaging agent. Its utility in fluorescence imaging, MRI, PET showcases its adaptability across diverse imaging modalities. By shedding light on biological processes, aiding in the diagnosis of cancer, and monitoring treatment responses, CUR contributes significantly to the field of bio-imaging. This dual role as both an anticancer agent and a bio-imaging tool offers exciting prospects for personalized medicine and precision oncology. As the convergence of oncology and imaging technologies continues to evolve, the integration of CUR-based strategies in cancer diagnosis and treatment is likely to play an increasingly vital role. The synergy between its therapeutic and imaging properties not only holds the potential to enhance our understanding of cancer but also to improve patient outcomes through tailored, precise approaches. In light of the ever-growing body of research and the constant pursuit of innovative solutions in cancer management, the future of CUR in both therapeutic and bio-imaging applications appears promising. However, continued research, clinical trials, and optimization of CUR-based formulations will be essential to fully unlock its potential and bring these benefits to patients worldwide. In summary, CUR's golden promise in the fields of oncology and bio-imaging is an exciting journey that continues to unveil new possibilities and deserves close attention from researchers, clinicians, and healthcare professionals alike. The insights gained from this review may guide future research directions, inspire new therapeutic strategies, and facilitate the development of more effective diagnostic tools. In the context of the broader scientific endeavor, the exploration of curcumin's dual roles highlights the importance of continued research into multifunctional compounds. It illustrates how integrating findings from diverse fields can lead to innovative solutions and advancements in healthcare. As such, the research presented here not only advances our knowledge of curcumin but also serves as a catalyst for future interdisciplinary investigations aimed at tackling complex medical challenges. This perspective reinforces the relevance of curcumin within the field and underscores its potential to drive progress in both scientific research and clinical practice.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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