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REVIEW ARTICLE

Tungsten Disulfide Nanomaterials (WS2 NM) Application in Biosensors and Nanomedicine: A review

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ABSTRACT

The development of nanotechnology has proposed new routes in the design of the novel device for medical and biological applications. Tungsten disulfide (WS_2) is a transition metal dichalcogenides. Tungsten disulfide nanomaterial (WS2 NM) are new nanostructures that can be used as a new option in bio-nanomedicine. Recently, Tungsten disulfide nanomaterial such as WS2 nanotubes, nanoparticles, quantum dots, and WS2 based nanocomposites have been used in some medical and biological science research. WS2 nanomaterial present chemical, physical, optical and electronic properties that can be exploited in a range of various applications. In this article, we discuss and report chemophysical relevant properties of tungsten disulfide nanostructures and the main achievements reached by using of this nanomaterial and related composite in biomedical research and biosensors, especially those involving electrochemical biosensors, optical biosensors, biomedical imaging, Photothermal therapy, radiotherapy, tissue engineering, and biocompatible anticancer and antibacterial agent.

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INTRODUCTION

In the last few decades, nanomaterials have been extensively used in a number of multidisciplinary science that include material science, environmental science, food industry, cosmetic, and medical sciences [1, 2]. The advantage of nanotechnology has increased our competence to develop the material's physicochemical properties to enable their use in biomedical applications such as diagnosis, drug delivery, nano-implants, bacterial treatment and cancer therapy. Various metal nanoparticles have been widely exploited for a wide range aforementioned goals [3, 4]. Recently, the synthesis and application of tungsten disulfide nanomaterials (WS2 NM) and related nanostructures in biomedical science increased, especially for diagnostic and treatment purposes [5, 6]. Tungsten disulfide (WS_2) is a member of group 6 transition metal dichalcogenides (G6-TMDs), including MoS2, MoSe2, MoTe2, WS2 and WSe2, which consist of two parts, first part is transition-metals (Mo,W,Nb,etc.) and second part is chalcogen elements (S, Se, Te) [7-9]. Tungsten (W) is the heaviest transition metal in the transition metal dichalcogenides (TMDCs) common family, also in comparison with the Mo, W is less toxic and inexpensive, for this reason tungsten have a high potential for a broad range of application in research and industry [10]. Tungsten

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Table 1. Electrochemical and optical biosensors base on tungsten disulfide nanomaterials

Biosensor	Biorecognition	Nanomaterial	Detection	Reference
Electrochemical	DNA	AuNPs/WS2-Gr nanostructure	impedimetric	[32]
	ferritin antibodies	tungsten disulfide -quantum dots	voltometric	[35]
	c-Met protein	(WS2 QDs)-AU	voltammetry	[34]
	Cell-based	(WS2/MWCNTs-OH)	impedimetric	[26]
	sulfamethazine(SMZ)	carbon quantum dots-tungsten disulfide nanocomposite glassy carbon electrode (CQDs-WS2/GCE)	voltometric	[36]
Optical	Cefixime residues in milk	tungsten disulfide quantum dots (WS2 QDs)	ratiometric fluorescent sensor	[33]
	Dopamine	WS2 QDs	fluorescent	[37]
	Nitrofurazone	Tungsten disulfide (WS2) Dot	fluorescent probes	[30]
	DNA	graphene coated surface plasmon resonance (SPR) sensor with Tungsten Disulfide (WS2)	SPR	[38]

disulfide as a transition metal dichalcogenides have superb electronic, thermal, magnetic, and optical properties due to its special structure [11-14]. Until now, several WS2 based nanomaterial with various structures (nanotubes, quantum dots [5], nanoparticles [15], nanotube [16], nanosheets [17], hybrid nanomaterial and nanocomposites [18, 19], etc.) were synthesized base on the special chemophysical structure of tungsten. The other hand, WS2 NM are widely interest for scientist among the medical research owing to their excellent optical activity, good conductivity, biocompatibility, less toxicity, which results from their high chemical and physical stability, as well as easy functionalization with organic and inorganic chemical and biologically active molecules or atoms [11, 13, 20-23]. Although WS2 NM has increasing been used in the medical research, there is no comprehensive review of their applications in nanomedicine. Therefore, in this review, we have summarized the available approaches of medical research applications of WS2 NM, as well as the used techniques in researches to evaluation of biological and medical effect of WS2 NM and discuss about achieved results.

BIOSENSORS

Biosensing systems

Biosensors developed as a combination of bio-receptors and transducers that are classified in accordance to their elements. These products are commonly divided into three categories based on transducers, including electrochemical, optical, and conductivity methods. Meanwhile, the classification of biomarkers is based on molecules, cells, and tissues (Fig. 1). Typically, the fabrication of a biosensor requires three steps as the following. The first step involves the reaction of the biomarker with the desired analyte, while the integration of a transducer occurs through the second step and the last step implicates the fixation/movement of a biological component to the transducer. It is considerable that the quality of these three stages and the currency of the components are incredibly effective in achieving successful results [24, 25].

The massive interest invested in biosensors is due to their speed and accuracy in the detection of small analytes. In line with this fact, the rate of combined biosensors with diverse nanomaterials and biomaterials for biomedical research has been extended. Recently, the products of nanobiosensor

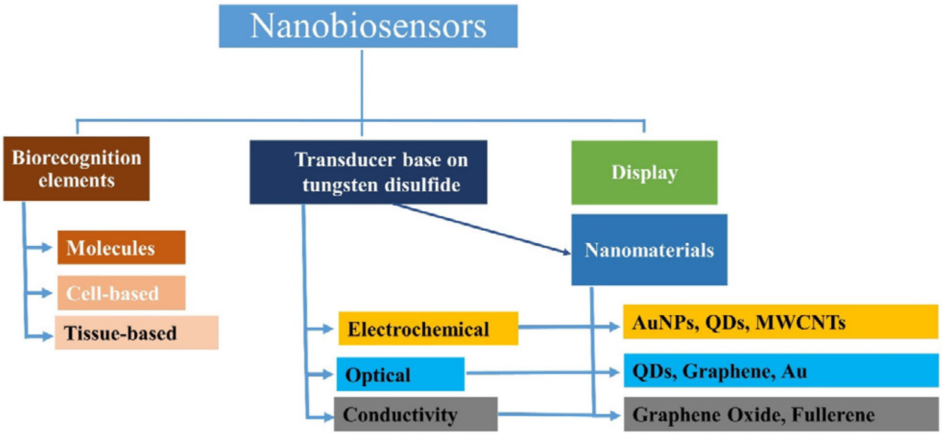

Fig.1. Nanobiosensor classification base on tungsten disulfide

presented a new route for the detection of biomolecular interactions [26]. An extensive amount of research was conducted on loading techniques and support carriers for designing and manufacturing electrochemical biosensors [27]. The quick development of nanomaterials into a significant research area was caused by their particular chemical and physical properties for producing biosensors with improved analytical performance [28].

Transducers are one of the vital components in biosensors that are responsible for exhibiting the responses of biomarker interactions with the target analyte through a recognizable and repeatable manner that requires the conversion of an specific biochemical reaction energy into visual structures. The high surface-to-volume ratio of nanomaterials is reasonable since transducers are accountable for the promoting a more accurate identification of biochemical reactions [26, 29]. Moreover, the electromechanical properties of nanoparticles can be an excellent aid for the biosensor technology.

The highly anisotropic bonding of WS2, which affects the electrical and mechanical properties, provided extremely interesting results in catalytic reactions [30]. Nowadays, researchers are focused on enhancing the sensitivity and specificity of biosensors by concentrating on the quality of nanobiosensor evolution and fabrication via surface modification, which implicate the application of different nanomaterials such as nanosheets [26, 31], nanoparticles [32] or quantum dot [33] in order to extend the affinity and improve signal amplification (Table1). The following sections present a summary of recent advances of using WS2 as a sensing platform for biomolecule detection by leveraging its optical and electrochemical properties, while particularly highlighting its applications throughout the sensing field.

WS2-based electrochemical biosensor

For a very long time, electrochemical biosensors, such as semiconductors and screen-printed electrodes, were used for various applications in numerous fields. In electrochemical based biosensors, the amplification of electrochemical signals by NPS leads to the development of several nano-hybrid compounds that are capable of contributing to the formation of strong biosensors as a quick, simple, and sensitive method for biomolecule identification. Electroactive metal tungsten (W) is extensively exerted in electrochemical biosensors. The electrical conductivity of WS2 can be improved by being combined with conductive compounds, similar to metallic nanoparticles such as gold, silver, and platinum, through the utilization of one-step or sequential electrodeposition techniques [34]. The superior sensing performance of proposed WS2-based sensor can be successfully employed for the observance of DNA hybridization, enzymes, and proteins, as well as environmental contamination and medical diagnostics [26].

In line with these facts, Ke-Jing Huang et al. presented a straightforward method for creating a robust and conductive interface for DNA hybridization based on electrochemical detection [32]. This study demonstrated a dual signal amplification platform that is built on the combination of tungsten sulfide–graphene (WS 2 –Gr) composite and Au nanoparticles (AuNPs). The obtained conductivity can be satisfyingly maintained by ssDNA-AuNPs/WS2-Gr, since the structures and characteristics of WS2-Gr and AuNPs cannot be altered by the DNA-mediated noncovalent assembly of this nanostructure. This dual signal amplification method can distinguish the single/ three-base mismatched DNA sequences with remarkable selectivity, which can facilitate the detection of target DNA down to femtomolar scale. Their linear range of detectable DNA concentration was fourfold more superior than the other methods.

In another study, a biosurfactant was used for biomolecule functionalization and providing the stability of tungsten disulfide quantum dots. [35]. Next to requiring a lower rate of toxic chemicals applications, their process exerted functionalized QDs for the purpose of ferritin antibodies immobilization. The results of this study indicated the achievement of a proper selectivity, stability, and dynamic linear range out of their immunosensor. These QDs functionalized electrodes proved to be quite applicable for the creation of portable or point-of-care devices. This platform can facilitate the observance of an extensive range of additional diagnostic indicators, which are medically important, by simply switching the target bio-receptor. However, the main obstacle to this approach is the availability of biosurfactants for synthesizing quantum dots. Therefore, it is necessary to scale up the manufacturing of biosurfactants.

The combination of QDs with nanoparticles results in a type of semiconductor that is used as an electrochemical modifier to improve the sensitivity of biosensors toward the detection of proteins. Ramin Pourakbari et al. developed a new biosensing technique for performing the quick and precise detection of c-Met protein by the exertion of tungsten disulfide quantum dots (WS2 QDs)-AU [34]. Their study implicated the modified electrochemical deposition of AuNPs, functionalized with WS2 QDs, on GCE (glassy carbon electrode). Thereafter, the immobilization of c-Met bacteriophage was carried out on the modified electrode to be applied for the detection of c-Met protein (colon cancer biomarker) via an electrochemical biosensor.

The characteristics of newly developed cell-based electrochemical sensors, such as the lack of labeling requirements, high sensitivity, simplicity, quickness, non-toxicity, and reusability, led to their robust application throughout in vitro toxicity assessments. Guanlan Wu et al. reported the usage of a simple method to create a hybrid material composed of WS2 nanosheets and hydroxylated MWCNTs (WS2/MWCNTs-OH) [26]. The substrate was a screen-printed carbon electrode (SPCE) with the advantages of requiring minimal costs, as well as being disposable and energy efficient. Modification with a WS2/MWCNTs-OH composite resulted in increasing the rate of sensitive and selective behaviors. The Grass Carp Kidney (CIK) cell line was exerted as an effective toxicology model for identifying and tracking the alterations of electrochemical responses throughout the assessment of cell viability. In this study, the application of cyclic voltammetry and high-performance liquid chromatography (HPLC) was considered to examine the electrochemical reaction mechanism of CIK cells. The cytotoxic effects of 2,4,6-trichlorophenol (2,4,6-TCP), polystyrene nanoplastics (PSNPs) and bisphenol AF (BPAF) were detected by the electrochemical sensor to be compared with the proposed sensor through the course of MTT assay. This sensor is practically applied for determining the cytotoxicity of genuine chemical wastewater samples.

Furthermore, Yan Wang et al. suggested the application of WS2-QD for the detection of sulfamethazine(SMZ) sensitivity through a label-free electrochemical aptasensing approach [36]. According to their experimental results, the idea of exerting electrochemical sensors can offer a straightforward, dependable, and efficient method for biosensing the trace of SMZ residue in environmental contamination monitoring and food safety detection. They also tried the application of WS2-QD for detecting sulfamethazine(SMZ) sensitivity via a label-free electrochemical aptasensing approach and achieved similar results to their previous work.

WS2-based optical biosensor

Upon the combination of an analyte and recognition components that lead to the formation of complexes, optical biosensors can provide the measurement of their surface's changes by the usage of optical instruments. Opcode-based fiber, evanescent wave fiber, resonant mirror, time-resolved fluorescence, interferometric, and surface plasmon resonance biosensors are among the different types of optical biosensors.

These biosensors can be categorized into two classifications of the direct and indirect optical biosensor. Direct optical biosensors require a complex on the transducer surface for signal generation, while indirect optical biosensors implicate fluorophores or chromophores as their labels to identify binding events and amplify the signal. Although higher signal levels can be produced through indirect biosensing techniques, however, they are limited by non-specific binding and a high reagent cost for the labeling process. Considering how tungsten disulfide (WS2) QDs can stand as applicable candidates due to their essential optical and electrical features, WS2 QDs exhibited excellent fluorescent properties [33].

WS2-QD was applied in colon cancer evaluation for the detection of c-Met protein in serum samples [34] as an efficient probe for dopamine fluorescence detection of dopamine (DA) [37]. Also, Mahsa Haddad Irani-nezhad et al. [33] introduced the usage of a ratiometric fluorescence sensor for the measurement of Cefixime based on tungsten disulfide quantum dots (WS2 QDs) and fluorescein (CEF). In this study, bulk WS2 was subjected to the combined sonication solvothermal procedure at a low temperature to create WS2 QDs. The suggested ratiometric probe was able able to configure the volume of CEF in various milk samples.

Moreover, Xinrong Guo et al. designed an optical biosensor that implicate a straightforward hydrothermal procedure for the production of luminescence from tungsten dots, which functions through sodium tungstate and reduced L-glutathione. Their biosensor involves the application of WS2 dots in the form of a fluorescent probe for the detection of nitrofurazone (NFZ) in nasal drops and water samples [30].

Recently, the attention of fundamental optical realizing electronics was attracted by Surface plasmon reverberation (SPR)-located biosensors on account of their hopeful applications in various fields such as healing diseases, biomolecules detection, biochemical discovery, and surroundings listening.

Parallel to this line of thought, it is noteworthy that graphene tiers can increase the sensitivity while decreasing the different conduct limits [38]. In this study, WS2 was inserted among the metal and graphene layers to increase the efficiency limits. An analysis was also performed on the thickness impact of gold on the experimental structure. Although the disparity of SPR angle for unsuited DNA strands is relatively insignificant, yet this phenomenon is notably countable for complementary DNA strands. Therefore, it can be stated that the suggested biosensor can provide a novel route toward the detection of biomolecular interactions.

Considering the ability of WS2 to specify a 2D covalent network, it is a suitable substrate for immobilizing biospecies. Pingyao Wang et al. reported the development of a fluorescent probe by using 2D WS2 nanosheets and aptamer-modified core-shell upconversion nanoparticles as the acceptor and donor, respectively[31]. This novel, sensitive, and selective biosensor can be applied for the rapid and specified quantification of E. coli. Furthermore, WS2 nanosheets can function as excellent energy acceptors due to containing a broad absorption spectrum that can increase the efficiency. Therefore, this fluorescent biosensor can be a platform for the observance of different bacterial pathogens through the alteration of related specific aptamer.

The conductivity of WS2 NM

Conductivity and development of basic structure conductivity for the design of biosensors is important. WS2 NM are shown excellent conductivity for use in electronic and biosensor device. Hexagonal crystals are the basic structural units of two-dimensional tungsten disulfide nanomaterials, in which two sulfur atoms are bounded with a tungsten atom that form the S-W-S sandwiched layer. The combination of S-W-S layers is caused by the weak van der Waals forces. Also, dormant is the substance of transition-metal sulfide phase. In contrast, the characteristics of WS2 nanosheets can be drastically altered by reducing their sizes down to the range of nanoscale, while their active sites are positioned at their edges. Hence, the shifting of the electron band gap occurs from 1.4 eV to 2.0 eV throughout the bulk phase of nanosheets. WS2 nanosheets succeeded in garnering the investment of many in various domains due to their vast specific surface area, fascinating electrical conductivity, and unique electronic structures. Therefore, it is crucial to find the ability to manage the size, morphology, and crystal structure of WS2 nanosheets [39].

Deqing Zhang et al. reported the usage of sodium diethyldithiocarbamate (as the reducing agent and sulfur source), tungsten hexachloride (as the tungsten source), and cetyltrimethylammonium bromide (as the surfactant) for synthesizing flat sheet-like tungsten disulfide that would contain a single crystal construction [17]. According to results, their facile, one-step hydrothermal route was successful in synthesizing the tungsten disulfide nanosheets. WS2 nanosheets contain a single-crystal construction with a distinctive lamellar and porous shape along with significantly high specific surface area and electronic criteria. A practical method for the enhancement of electromagnetic shielding efficacy is the addition of conductive nanotubes to an insulating polymer matrix. The work of Jan Macutkevic et al. claimed that due to the high aspect ratio of nanotubes, their addition to an insulating polymer matrix can effectively increase the electromagnetic shielding performance [40]. Apparently, WS2 nanotubes and polymer matrixes contain relatively ohmic electrical connections.

Over the last few decades, a massive effort was paid into the production of innovative nanostructured hosts in order to improve cathode electronic conductivity and decrease the loss of soluble polysulfide intermediates. Notably, several carbon materials, with outstanding electronic conductivity, high specific surface area, and controlled construction, were able to successfully function as a sulfur host or conductive framework. Non-polar carbon-based compounds can improve the application of sulfur by facilitating the transportation of ions and electrons. Considering its mono-atomic sheet of carbon atoms, graphene is a popular (2D) substance among various carbonaceous materials. Weishan Li et al. reported the development of a coral-like reduced graphene oxide/tungsten sulfide hybrid in the form of a host for sulfur cathode at the University of Bristol [41]. This hybrid can prepare a 3D network for electronic conductivity and a large surface area for the chemical entrapment of intermediates. Their work presented the design of porous, 3D coral-like rGO/WS2 composite by using a facile hydrothermal process to be exerted in the form of a cathode host for LSB. The notable potential of this composite for the discovery of high energy density and energy storage devices is undeniable.

On the other hand, the optical activities and electrical properties of atomically thin 2D metal dichalcogenide (TMDCs) materials, such as WS2 and their composites with graphene or graphene oxide, attracted the attention of researchers in recent years. Jaesool Shim et al. reported the successful preparation of a core-shell reduced graphene oxide (rGO) on tungsten sulfide (WS2) nanostructure that was capable of catalyzing the four-electron oxidation-reduction reaction (ORR) in a 1 M KOH aqueous solution [42]. According to their results, nano-electrochemists provided the enhancement of a straightforward and super-efficient electrocatalyst by the exertion of an uncomplicated microwave irradiation procedure. They performed an assessment on the activity and stability of produced catalyst throughout methanol oxidation reaction and ORR in alkaline media.

Yuhua Xue et al. disclosed a one-step hydrothermal process for creating a novel core-sheath fiber with a graphene core and radially aligned tungsten disulfide sheath. An all-solid fiber-shaped supercapacitor was created by using two of these fibers as electrodes. They reported the ability of the sheath nanosheet array in generating numerous active sites and facilitating the occurrence of quick ion diffusion, while the high conductivity of fibers can be ascertained by the graphene core. The existence of extended capacitance, long-term stability, and exceptional flexibility in an electrode material can result in a unique contender for creating high-performance energy storage fibers [19].

A new allotropic form of carbon with stable 60-atom molecules was discovered in 1985 and labeled as “fullerene”. The development of inorganic fullerene-like nanoparticles was driven by the intense interest in the distinct physical and chemical features of fullerene-like nanoparticles (IF-NP). These potentially unstable structures can bend and close in on themselves under specific circumstances, leading to the attachment of rim atoms and resembling graphite, while generating particles in the size range of 20 to 200 nm. The identification of this molecule sparked an active investigation into other potential carbon configurations. Considering their unique structures, MoS2 and WS2 nanoparticles proved to be excellent solid lubricants capable of improving friction and wearing throughout wet and dry environments with varying loads. In the report of Alberto De Stefani et al., orthodontic stainless steel wires were coated with the lubricant-containing nanoparticles of molybdenum and tungsten disulfide (MoS2 and WS2) to check the chances of causing improvements in the tribological qualities during the sliding of wires over the brackets [43].

They reported the relative reasonable cost and effectiveness of this approach in comparison to disulfides based on their characteristics and behavior.

BIOIMAGING AND RADIOTHERAPY

The WS2-QD (3 nm and28 nm) synthesized as enhancer for X-ray computed tomography (CT)/ photoacoustic imaging (PA) due to its high atomic number and NIR absorption. Smaller particles temperature increase had higher temperature raise with NIR irradiation, therefore are better candidate for PTT. In vitro toxicity of WS2-QD on HeLa and HepG 2 cells in different concentration showed cell viability higher than 85% for both cell lines. In vivo toxicity evaluation on mouse didn't show any sign of deviation in body weight, eating, drinking and normal activity. Biodistribution assessment showed accumulation in kidney, liver and spleen with no significant hepatic and renal dysfunction and after 30 days. Comparison between NIR alone, X-ray alone to NIR+WS2 and RT+WS2 treatment on 4T1 cell showed cell viability reduction to 97% and 75% in NIR alone and X-ray alone respectively and reduction to 39% and 31% in NIR+WS2 and RT+WS2 respectively. Synergic effect of using RT/ PTT reduced cell viability to 6%. Effectiveness of a radio-sensitizer to tumor proliferation reduction measured by the sensitizer enhancement ratio (SER). For WS2-QDs SER reported 1.22 and increased to 1.31 in combination with NIR. WS2 QDs + NIR+ RT showed complete elimination of tumor in 5 days after treatment. WS2 QDs were intravenously injected into the tail vein of BEL-7402 tumor-bearing BALB/c nude mice to investigate the photoacoustic (PA) signal of tumor at different time. After injection PA signal reach twice compared to before injection and lasted for 24 h. To investigate CT contrast performance in vitro, WS2-QD compared to iopromide. WS2-QD showed two times higher performance at the same concentration. To investigate CT contrast in vivo increased from 153±4.2 to 332.7±27.4 after WS2-QD were injection to BEL-7402 tumor-bearing BALB/c mice. Results indicate that WS2-QD is an excellent contrasting agent for CT and PA dual-modal imaging and synergistic therapy [5]. Nanomaterials have shown excellent potential in bioimaging. Design of new nanomaterial for Non-invasive monitoring is an attractive field in nanomedicine. Li et al. designed MPDA-WS2@MnO2 to use in CT/MSOT (multispectral optoacoustic tomography)/MR imaging modalities. Polydopamine (PDA) - WS2@manganese dioxide (MnO2) nanocomposites has good biocompatibility and photothermal stability. Manganese dioxide (MnO2)-based nanostructure produce Mn+2 ions which result in pH/H2O2-responsive activated T1-weighted MR signal. To investigate in vitro efficacy of MPDA-WS2@MnO2, by the 808 nm NIR laser at 1.5 W/cm2 irradiate on it. Cytotoxicity of MPDA-WS2@MnO2 on 4T1 cells under 808 nm laser irradiation were done and at the highest concentration most cells were killed however no significant cytotoxicity was observed without laser irradiation even at highest concentration. MPDA-WS2@MnO2structure showed SER up to 1.562 which had an increase compared to MPDA-WS2 nanoparticles and confirm enhancement in sensitivity of tumor cells to X-ray due to O2 generation. To investigate photoacoustic signaling at 808 nm different concentration of MPDA-WS2@MnO2 in different time interval and reached maximum level at 12 post-injection and showed 2.55-fold enhancement. Finally results shown that excellent achievement for imaging and thermoradiotherapy of hypoxic cancer [44].

PHOTOTHERMAL/ RADIATION THERAPY

Radiation Therapy is one of the methods to combat cancer and photothermal therapy (PTT) is a subset of radiation therapy in which use photosensitizer material to convert light to heat and ablate cancer cells. In this method a specific range of wavelength which is called Near-Infrared (NIR) radiate on PTT agents In 2019 Lellouche et al. used tungsten disulfide (WS_2) nanocomposite as a PTT agent. WS_2 nanocomposites were functionalized by ceric ammonium nitrate–maghemite (CAN-mag) nanoparticles for three reasons : (1)enhance magnetization properties of WS_2-NT, (2)ability for second functionalization with polymers such as polyethyleneimine (PEI), Polyacrylic acid (PAA) and other molecules to increase therapeutic activities, (3) to reduce aggregation of WS_2-NT. WS_2-NT had diamagnetic properties on the other hand CAN-mg due to presence of iron-oxide nanoparticle had superparamagnetic activity . Photothermal therapy of WS_2-NT and WS_2-NT-CM were testing on Hela (cervical cancer) and MCF7 (breast cancer) cell lines by a 700 nm NIR laser. WS_2-NT treated Hela cells showed, 65% and 20% of cells dead, and detached respectively and in WS_2-NT treated MCF7 cells 50% were dead and 50% were detached. On the other hand, WS_2-NT-CM treated Hela cells showed 95 % dead and 5% detachment and WS_2-NT treated MCF7 cells showed 85 % dead and 15% detachment. The reason of this difference is that WS_2-NT-CM accumulate in and near cells while WS_2-NT aggregate walls of blood vessels and cannot reach the tumor [6].

Jiang-Tao Wang et al. used one-step 'bottom-up' hydrothermal reaction to synthesize tungsten disulfide with PEGylated coat (WS_2-PEG) nanoparticles for CT-guided PTT in Murine breast cancer cells (4T1 cell line) and balc/c mice that bear 4T1 cell line which were subcutaneously injected. Photothermal stability was compared to indocyanine green (ICG) by the 808 nm laser (2 W/Cm^2) 5 min irradiation with several cycles and showed good stability while ICG disintegrated. 4T1 cells with WS_2-PEG and irradiated by the 808 nm laser (2 W/Cm^2, 5 min) showed a cell viability drop to 5%. CT imaging and PTT in vivo investigation showed a stability in temperature at 52 for that local temperature in 4T1 cell bear mice treated with WS_2-PEG NPs and laser led to no sign of increase in tumor volume after 3 days also due to x-ray attenuation of tungsten atoms it can play contrast agent role for CT-imaging tumors. Comparisons between control group and group that received WS_2-PEG NPs in spleen, kidney, liver, lung and heart showed no difference and there was no significant weight-loss in NPS received mice. Result showed in biocompatibility low cytotoxicity of WS_2-PEG NPs [45].

WS2 NM BASED Nanocarriers

Traditional drug delivery systems like oral and injection needed higher concentration of drugs to see therapeutic effect and administration this amount of drugs led to side effect in some patients. Recently controllable stimuli-responsive drug delivery systems which use of magnetic field, enzyme, ultrasound, light, pH or electrical stimulations developed. Hsiao et al. design an electric responsive delivery system using WS2 due to their suitable electrical properties. WS2 synthesis and functionalized by ligands which were thiol-terminated like thioglycolic acid (TGA), dimercaptosuccinic acid (MSA), and 2-ethanethiol (2ET) then non-covalently coated with polypyrrole (PPy) which is electrically conductive and for drug model 5-fluorouracil (5-FU) were choose. TGA-WS2-PPy exhibit higher drug release (90%) compared to MSA and 2TE due to swelling effect. Cytotoxicity of TGA-WS2-PPy-FU on HaCaT cells in the absence of electrical stimulation showed no significant toxicity; however, under electrical stimulation, HaCaT cells died. To investigate in vivo drug release two patch were place on control group and other with drug and Raman mapping was performed to assess carrier penetration to skin. Results showed deeper penetration to skin under electrical stimuli in delivery system make this novel carrier appropriate candidate for externally-controlled model [46].

Sobhani et al. used design a dendrimers grafted Poly (N-Vinylcaprolactam) modified WS2 nanosheets as a thermosensitive nanocarrier for Pioglitazone delivery. The synthesized structure were evaluated in simulated human blood fluid for in vitro treatment of diabetes. 18% and 98% of total drug were released in vitro within the 6 h at 37 C and at 50 C without IR irradiation, respectively. However drug released reached up to 100% of in presence near-infrared laser irradiation from modified WS2 nanocarrier within 15 minutes [47].

WS2 NM IN TISSUE ENGINEERING AND IMPLANT

Nanomaterial can be used to tissue engineering for fabrication of high performance scaffold, implant and medical device. The WS2 nanomaterial are novel candidate for the development of tissue engineering and nanomedicine. Due to electrical and mechanical properties of tungsten disulfide (WS2) they can be used in scaffold reinforcement, design in tissue engineering and drug delivery [5].

In orthodontic treatment tooth movement along archwire generates friction force between wire and bracket in opposite direction of orthodontic force. In the past the focus was on engineering bracket nowadays Lowering friction force is the main focus and can result in lower treatment time and risk of root resorption. For this purpose hexagonal structure (H) of molybdenum and tungsten disulfides (MoS2 and WS2) are suitable candidate due to excellent solid lubricant properties also in certain condition they can bend on themselves and create graphite-like structures. Burono et al. studied on coating effect of stainless steel (SS) with three groups of Ni, Ni+MoS2 and Ni+WS2 with Damon Q and In-Ovation self-ligating bracket and two different angles (0 and 5) for wire-bracket in dry and wet conditions. Nanoparticles were coated on the steels with electrodeposition method due to being controllable and to simulate wet condition, artificial saliva was used. Coating thickness was reported 10µm, 20 µm and 15µm for Ni, Ni+MoS2 and Ni+WS2 respectively. Not seen any sign of breakage at minimum binding but only Ni coated wire remains without damage at maximum binding in groups. Coating steels with nanoparticles showed more decrease in friction value compared to Ni-coated steel but there were no significant difference between Ni+WS2 and Ni+MoS2, latter showed lower decrease. In conclusion Ni+WS2 and Ni+MoS2 showed better features compared to neat stainless steel or Ni-coated Steel and significant reduce in fraction between archwire and In-Ovation bracket (not Daman Q) in dry condition [48]. Orthodontic stainless steel wires developed by using fullerene-like WS2. Redlich coated stainless steel (SS) with nicke-phosphorus and inorganic fullerene-like tungsten disulfide (WS2) with electroless deposition. Friction coefficient exhibit notably decrease from 0.25 to 0.08 and fraction forces decreased by up to 54%. Also chemophysical analysis and imaging demonstrate attachment of Ni-P with IF-WS2 nanoparticles on stainless steel after extensive friction test . Kornfield et al design a nanocomposite of WS2 and Poly(L-lactide) (PLLA) for bioresorbable vascular scaffolds (BVS) .PLLA is first clinically approved polymer for BVS manufacturing and degrade to lactic acid which is non-toxic material for body and has so many applications in drug delivery, food packaging and biomedical devices. Although PLLA-based polymers have twice thickness than metal stents but they are fragile, so there is a need to reinforce their strength without adding to its thickness. WS2 nanoparticles have excellent mechanical properties and flexibility and can increase PLLA strength. PLLA-WS2 composites were prepared by addition 0.05wt% of WS2 to PLLA and solvent casting then hot press method. Mechanical properties of composite was investigated by subjecting WS2 to uniaxial stretching at 500mm/min stretching rate at 90 c temperature. Up to 100% strain was shown in stress-strain profile of both nanocomposite and neat polymer. Spectroscopy analysis confirm WS2 nanotubes act as nucleation center and increase crystallinity [49].

Aging is one the challenges that humans are faced and bone fractures especially due to osteoporosis is one big problem. Developing biocompatible material to use in bone tissue engineering is a solution, but most of them don't have adequate mechanical properties, their degradation rate is uncontrolled and lack bioactivity, so there is an urge to produce better material. In TMDCs, tungsten disulfide (WS2) has shown good biocompatibility, physical and photoelectrochemical properties. Chen et al. used chlorophyll molecules to synthesize WS2 nanosheet with liquid-phase exfoliation method then mixed them with polycaprolactone (PCL)/calcium silicate (CS) to produce biocompatible composite. Chlorophyll assisted WS2 synthesis shown better stability than chlorophyll-less exfoliated WS2. WS2/PCL/CS composite didn't show any toxicity and due to their macro-pore structure improve nutrient transportation, cell in-growth and leading to osteogenesis and angiogenesis. Compared to PCL/CS alone WS2/PCL/CS exhibit an increase in young's module from 32 MPa to 145 MPa and enhancement in compression strength from 2 MPa to 6 MPa. In vivo bone regeneration study exhibit a 120% compared to commercially MTA material and 300% mechanical properties enhancement compared to PCL/CS and resulted that WS2/PCL/CS is an excellent candidate in bone regeneration composites [50].

Lalwani et al. used 0.01-0.2 wt.% concentration of tungsten disulfide nanotubes (WSNTs) to reinforce poly(propylene fumarate) (PPF) composite and compared it to SWCNT and MWCNTs. WANT-PPF improved mechanical properties compared to neat PPF in all concentrations compared to SWCNTs and MWCNTs. WSNTs showed notable enhancement in mechanical properties and high crosslinking density, uniformity and no aggregation while dispersed into polymer matrix compared to SWCNT and MWCNT which had micron sized aggregation in PPF matrix result in being excellent candidate for application in tissue engineering [51].

BIOCOMPATIBILITY OF WS2 NM

Biocompatibility of Tungsten Disulfide Inorganic Nanotubes and Fullerene-Like Nanoparticles with Salivary Gland Cells. Impairment in salivary gland function lead to oral disease and there is no sufficient treatment for this disease. Aframian et al. investigate biocompatibility of WS2 in Salivary gland cells. In research multiwall inorganic nanotube (INT-WS2) and inorganic fullerene-like nanoparticles (IF-WS2) were synthesized in high temperature using reactor. Toxicity of both groups were evaluated by A5 and RSC cells in different concentration 0.22 µg/ml to 35.2 µg/ml and 35.2 and 100 µg/mL for

INT-WS2 and IF-WS2, respectively. Both cell line didn't show significant difference in kinetic, proliferation, viability and morphology also these particles were seen in cytoplasm of cell and not in nuclei with a membrane surrounding them indicate endocytosis mechanism of them, therefore this particles are biocompatible and can be used in medical applications [52].

WS2 IN DRUG DELIVERY AND THERAPEUTIC AGENTS IN CANCER THERAPY

Preparation of stable and biocompatible nanomaterial and nanocomposite for drug delivery is a basic challenge in nanomedicine. Providing new safe nanomaterial with drug delivery capability is an important issue in medical nanotechnology. It seems that SW2 related nanomaterial are suitable candidate for this purpose. Recently many research carried out about this subject.

Kasinathan et al. synthesis chitosan functionalized WS2 nanocomposite implanted with ruthenium nanoparticles (CS/WS2/Ru). Being biocompatible and non-toxic chitosan is an excellent candidate in drug delivery systems. On the other hand, due to small size and large surface area WS2 can improve biological features of chitosan. Ruthenium is a part of noble metals have a wide range of medical applications from biosensing to pharmaceuticals. Due to being toxic to fungi, bacteria, and viruses, Ru is a good option to development of anti-pathogenesis drugs. In vitro cytotoxicity of CS/WS2/Ru nanoparticles was investigated on Vero cells with different concentration. Results shown minimum toxicity which can be negligible and consider it non-toxic. Antibacterial activity of nanoparticles was studied on B.subtilis, S.aureus as Gram (+) and K.pneumoniae, E.coli as Gram (-) bacterial group via with different concentration of nanocomposite. Results indicate oxidative stress generated by chitosan functionalized WS2 nanosheets play a vital role in antibacterial activity. It was observed that Ru enters the cytoplasm and interacts with protein and DNA, causing cell death. MCF-7 breast cancer cell line was chosen to investigate anticancer activity of CS/WS2/Ru in different concentrations compared to control groups. In 100 µg/ml CS/WS2/Ru nanocomposite showed higher cell inhibition. W^{+4} and Ru^{+3} positive charge play role in disruption of cell membrane and mitochondrial dysfunction, ROS production and oxidative stress act as pathway for cytotoxic effect in cancer cells and prove anticancer activity of composite [53]. In another study Kasinathan et al. used CS/WS2/Pd to investigate antibacterial and anticancer activity. Bacterial groups and cancer cell lines which were subjected to nanoparticles were the same as their previous study. Antibacterial of CS/WS2/Pd nanostructure were tested on Gram (+) and Gram (-) bacterial groups and inhibition zone in 100 µg/ml concentration was assessed. Maximum inhibition was observed for E.coli. In vitro cytotoxicity of nanoparticles was evaluated on Vero cells with different concentration and shown negligible toxicity. Also, in 100 µg/ml CS/WS2 and CS/WS2/Pd nanomaterial showed 70.15% and 73.24% MCF7 cancer cell inhibition respectively. Consequence showed W+4 and Pd+ positive charge effectively attached to negative charge cell membrane and play a role in its destruction [20]. Gnatyuk et al investigate anticancer activity of WS2 nanosheet on Lewis lung carcinoma cell. WS2 nanoparticles didn't show any sign of toxicity to cancer cells in the day 1 of incubation but prolongation of this time up to 2 days result in a concentration-dependent decrease in cell viability more than 30% with maximum cytotoxic effect at nearly 2 µg/ml of WS2 this was due to entering tumor cells or accumulate on their surface in longer period of incubation time [54]. Tamayo-Ramos et al investigate toxicity of three groups of commercially WS2 on adenocarcinomic human alveolar basal epithelial cells (A549 cells) and Saccharomyces cerevisiae. WS2-ACS-M with lateral size from 100 nm to 4 µm (microdispersion), WS2-ACS-N with a range from 20-500 nm (nano dispersion) and WS2-ACS-N-PW which is dry powder form. Aqueous dispersion contains 1T'-WS2, 2H-WS2, WO3 and SO2. A549 cells were subjected to different concentrations of nanoparticles to assess ROS generation in cells resulted in a low level of ROS in treated cells exhibiting no toxicity. Toxicity test on S. cerevisiae in 160 mg/L and 800 mg/L concentration was done. After 2h there was no sign of toxicity however, after 24 h there was a decrease in cell viability. In 160 mg/L treated S. cerevisiae, WS2-ACS-M reduction was more significant compared to WS2-ACS-N however in 800 mg/L concentration WS2-ACS-N exhibit more decrease compared to WS2-ACS-M. Same assessments were done on aqueous solution of WS2, which was prepared by dry powder form and were able to show a similar toxicity effect on S. cerevisiae cells [55].

CONCLUSION & FUTURE PERSPECTIVE

The purpose of this review was to consolidate existing research information on the WS2 based nanomaterial for application in various fields of nanomedicine. The obtained results show that WS2 nanomaterial and related nanocomposites are biocompatible and can be a significant approach for the use in biosensor, bioimaging, dental and orthopedic implant, controllable drug delivery, tissue engineering, cancer therapy, Photothermal and Radiation Therapy. Considering the chemophysical structure, optical and electrical unique properties and wide potential of tungsten nanomaterial, these nanoparticles can be considered as a solution to overcome a lot of problems in the field of medicine and pharmaceuticals in the future. The other hand, better understanding of fundamental of WS2 nanomaterial and their interaction with biomolecules and cell or organs, moreover functionalization of SWS2 NM by biomolecules could help researcher and medical scientist to developed the new nanostructures and nanocomposites with high efficient and applicable in nanomedicine in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest .

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