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REVIEW

Advancements in Nanomedicine for the Diagnosis and Treatment of Kidney Stones

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Abstract: Kidney stones constitute a common condition impacting the urinary system. In clinical diagnosis and management, traditional surgical interventions and pharmacological treatments are primarily utilized; however, these methods possess inherent limitations. Presently, the field of nanomedicine is undergoing significant advancements. The application of nanomaterials in biosensors enables the accurate assessment of urinary ion composition. Furthermore, contrast agents developed from these materials can improve the signal-to-noise ratio and enhance image clarity. By mitigating oxidative stress-induced cellular damage, nanomaterials can inhibit the formation of kidney stones and enhance the efficacy of drug delivery as effective carriers. Additionally, by modifying the physical and chemical properties of bacteria, nanomaterials can effectively eliminate bacterial presence, thereby preventing severe complications. This review explores the advancements in nanomaterials technology related to the early detection of risk factors, clinical diagnosis, and treatment of kidney stones and their associated complications.

Keywords: nanomaterials, kidney stones, oxidative stress, biomaterial

Introduction

Kidney stone disease (KSD) is one of the most common diseases of the urinary system, which refers to the formation of hard deposits composed of minerals and salts inside the kidney.[1–3] The incidence of kidney stones is related to geographical, socioeconomic and climatic factors. In addition, genetics,[4] age, gender, ethnicity, and diet also influence the incidence of the disease. The global prevalence of this condition ranges from 2% to 20%, with a recurrence rate of approximately 30%-50% over a span of five years.[5,6] Consequently, it has emerged as a significant public health concern[7] (Figure 1).

Kidney stones are mainly caused by supersaturation of certain metabolites and minerals in the urine. When the concentration of calcium, oxalic acid, uric acid and other substances in urine is too high to exceed its solubility in urine, supersaturation will form and urine crystals will appear. This occurs mainly in patients with kidney stones. The persistence and constant accumulation of urinary crystals increases the risk of developing kidney stones.[8] The metabolic process of crystals is often closely related to the concentration of various ions in urine,[9] such as calcium ions, oxalate, urate and phosphate,[10–12] which can promote the crystallization and aggregation of stone components.[9] Pyrophosphate and citrate can inhibit the formation of stone crystals, so early detection of related ions can effectively intervene in the occurrence and development of kidney stones.[13,14] The most commonly used imaging methods for clinical evaluation of kidney stones include: urinary ultrasound, urography (KUB), computed tomography (CT), magnetic resonance imaging (MRI) and intravenous urography.[15] Each method has brought great convenience to the diagnosis and treatment of patients with suspected kidney stone diseases, and further development of these imaging modalities to enhance the ability of clinicians to accurately and safely manage patients with kidney stones will be helpful in the future. Treatment of kidney stones usually consists of medical and surgical treatment.[16,17] Medical therapy includes alpha-blockers, calcium-channel inhibitors, and phosphodiesterase type 5 (PDE5) inhibitors. In patients with uric acid stones, the stones can be

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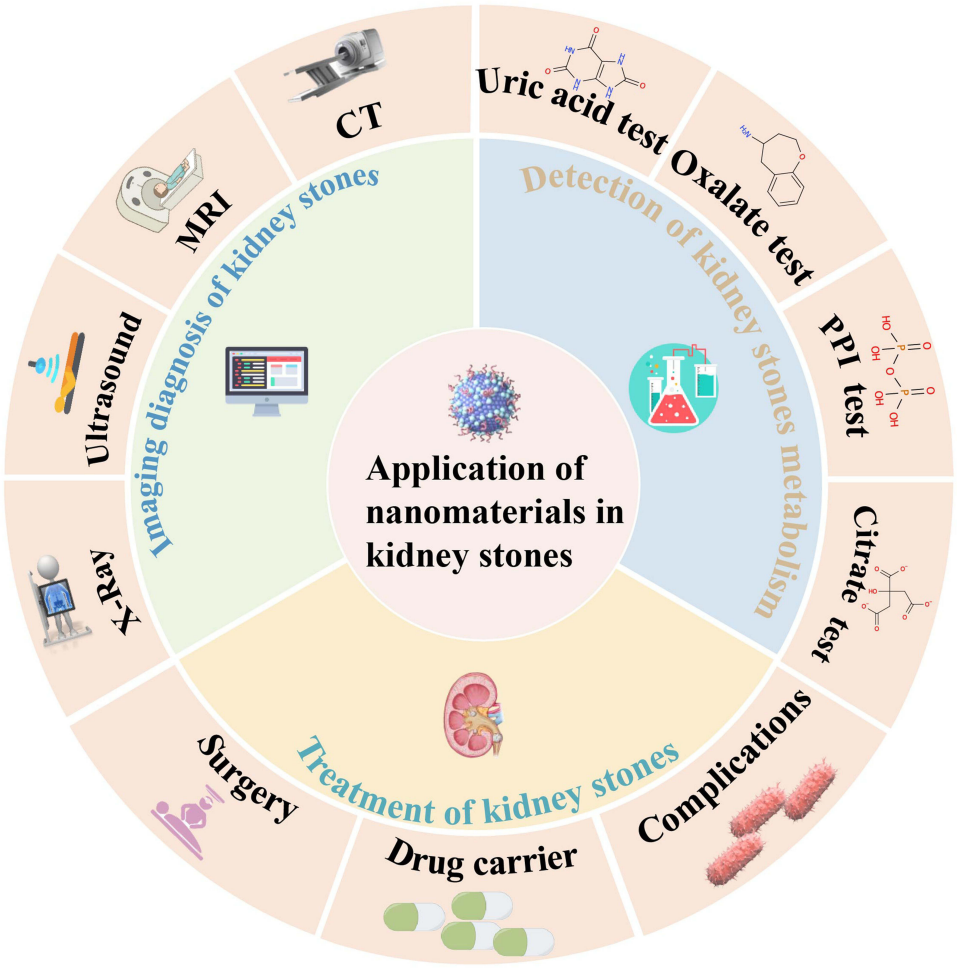

Figure 1 Schematic diagram of the application of nanomaterials in the diagnosis and treatment of kidney stone diseases.

dissolved by alkalinizing the urine with potassium citrate. However, due to the lack of good delivery, many stone-inhibiting drugs are difficult to achieve satisfactory results due to short residence time and low bioavailability. Therefore, effective drug delivery is very important. Surgical treatment includes extracorporeal shock wave lithotripsy (ESWL),[18] ureteroscopic lithotripsy (URS), percutaneous nephrolithotomy (PCNL), laparoscopic lithotripsy[19] and, less commonly, open surgery.[20] However, there are still a considerable number of patients with residual stones and postoperative complications. Except for those who actively receive treatment, most patients in the real world do not attract enough attention in the early stage of kidney stone disease, but this just increases the probability of other complications. When kidney stones block the ureteropelvic junction, they can cause severe back pain, hematuria, vomiting, and painful urination.[21] Long-term progression can lead to urinary tract infection,[22] sepsis,[23] urinary tract obstruction and renal failure,[24] renal cancer,[25] and cardiovascular and cerebrovascular diseases.[26]

Nanoparticles play an important role in modern scientific research, especially in biomedicine.[27–31] Nanomaterials usually refer to at least one dimensional structure size in the nanoscale (1–100nm),[32] which has special thermal, biological and electromagnetic properties different from general materials,[33–37] such as surface effects, quantum size effects and macroscopic quantum tunneling effects.[38] Based on their composition, nanoparticles are generally classified into two broad classes: organic and inorganic. (Figure 2) Specifically, organic nanoparticles include polymer vesicles, dendrimers, polymer micelles, nanospheres, nanohydrogels, liposomes, and lipid nanoparticles, among others. These organic nanoparticles are widely used in drug delivery, gene therapy, and vaccine development due to their good biocompatibility and tunable physicochemical properties.[39,40] Inorganic nanoparticles, on the other hand, include metallic nanomaterials and non-metallic nanomaterials. Metal nanoparticles such as gold, silver, and iron oxides are often used in

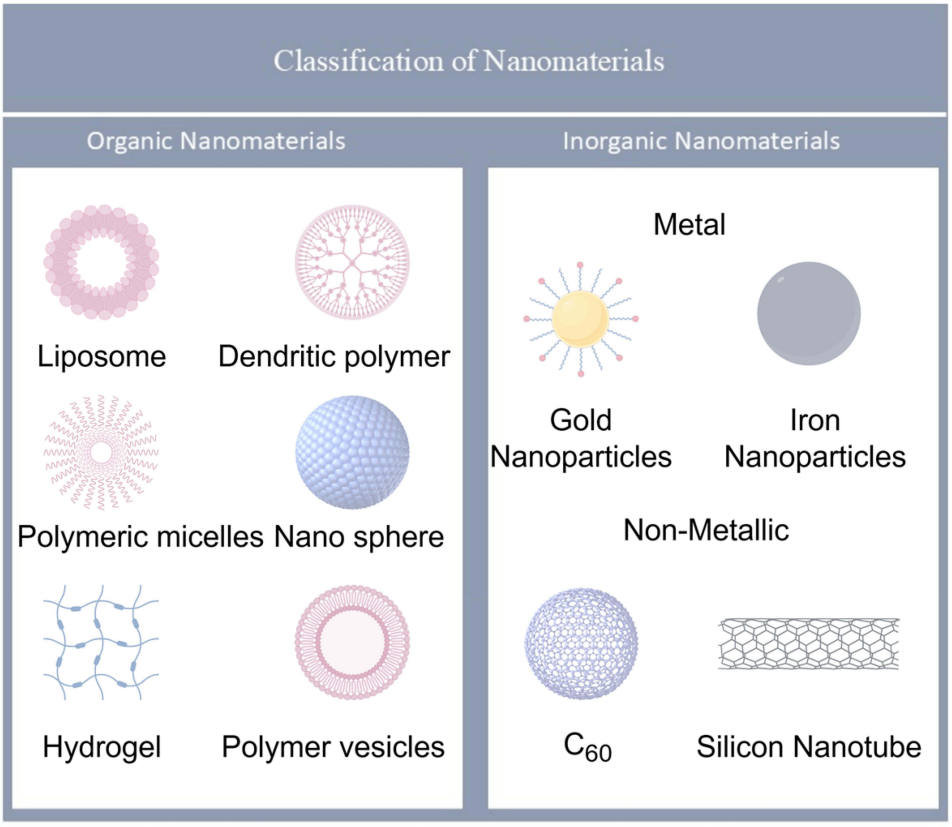

Figure 2 Classification of nanomaterials.

applications such as biological imaging, targeted drug delivery, and cancer therapy due to their unique optical and electrical properties.[41,42] Non-metallic nanomaterials such as carbon nanotubes and graphene can provide support for cell growth and tissue repair due to their excellent mechanical performance.[43,44] Inorganic nanomaterials are synthesized in a variety of ways, including bottom-up and top-down strategies, which allow researchers to precisely control the shape, size, and surface properties of nanoparticles to optimize their applications in biomedicine.[45,46] In addition, the combinatorial forms of nanoparticles have attracted much attention. For example, lipid-polymer hybrid nanoparticles combine the advantages of organic and inorganic materials and are able to improve drug bioavailability and targeting.[47,48]

In the field of drug delivery, nanoparticles can efficiently load drugs[49–53]precisely regulate the release characteristics of therapeutic drugs, and improve the efficacy of drugs;[54] In the detection of disease-related biomarkers: biosensors based on carbon nanotubes or graphene can detect biological molecules such as glucose and cholesterol in blood.[55,56] In the field of targeted therapy, anti-EGFR antibody can be modified on the surface of nanomaterials to achieve active targeting of tumor cells against the overexpressed epidermal growth factor receptor(EGFR)on the surface of tumor cells.[57] Biocompatibility: By controlling the size of nanomaterials, they can be more easily taken up and metabolized by cells.[58] Magnetic nanomaterials in biomedical imaging can improve the resolution of tissue and cell imaging.[59,60] The use of nanoparticles in immunotherapy can better effectively transport antigens to antigen-presenting cells, thereby enhancing the immune response.[61] In addition, chronic inflammatory diseases and regenerative medicine are also widely used.[49,62,63]

Nanomaterials have shown extraordinary potential in the diagnosis and treatment of kidney stones. Using the characteristics of nanomaterials to make a biosensor with high sensitivity to detect the relevant ion concentration in urine fluid,[64] the early monitoring and management of kidney stones can be realized. Nanomaterials can enhance the contrast of images and improve the imaging clarity of tissues. Nanoparticles can be used as effective drug carriers to protect renal tubular epithelial cells from oxidative stress damage and inhibit the occurrence of stones.[65,66] The

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photothermal and photoacoustic energy generated by nanomaterials can be used to dissolve stones and improve stone clearance efficiency. Hydrogel nanomaterials can reduce the residual rate of stones.[67] In the treatment of kidney stone complications: nanotechnology reduces the possibility of stone-related infections by precisely targeting the removal of biofilms and bacteria on kidney stones.[68] Biomimetic nanoparticles have shown promise in improving the survival of patients with sepsis,[32] and can also be used as effective carriers of antibiotics to enhance bacterial clearance and infection control.[69,70] In addition, nanomaterials can promote arterial wall remodeling and reduce the surgical risk of massive bleeding caused by accidental vascular injury during open surgery.[71]

Application of Nanomaterials Technology in the Detection of Kidney Stone Metabolism

Timely detection of related ions in urine can effectively intervene the occurrence and development of kidney stones. One of the most effective ways to detect urine ions is as a biosensor, and the unique chemical composition and crystal structure of nanomaterials play a crucial role in the electrochemical sensing performance. Quantum dots (QDS), as a semiconductor nanostructure with a diameter between 2–10 nm (10–50 atoms), are very popular in the field of sensing because of their wide width, symmetry, size-tunable emission spectrum, wide absorption spectrum, long photonics lifetime and significant photostability properties.[72,73] It can distinguish metal ions of different valence states by fast and efficient cation exchange reaction with metal ions at room temperature.[74] At the same time, the fluorescence quenching effect during the exchange process lays the experimental foundation for the construction of homogeneous fluorescence analysis. Nitrogen-doped carbon quantum dots (N-CQD), in which N atoms are doped into the structure of CQDs, form N-containing functional groups on the surface of CQDs,[75] which show strong water solubility and electrochemical activity.[76] There are strong cathodic and anodic ECL signals in the sensor.[77] VS_2 nanoflower structure, this 3D layered architecture provides a large surface area and abundant active sites that contribute to the adsorption and oxidation of oxalate on the electrode surface. Its high crystallinity ensures efficient electron transfer and enhances the conductivity of the modified electrode. The presence of V^{4+} and S^{2-} in their respective oxidation states contributes to the electrochemical activity and stability of VS_2 nanoflowers, making them more suitable for electrochemical sensing applications.[78] $FeMoO_4$ nanospheres with rough surface had better peroxide-like activity (V max=28.47×10-8Ms-1) and substrate affinity (Km = 0.174 mm) for H_2O_2. The combination of Fe and Mo ions will avoid the instability of the free Fe^{2+} state and at the same time have a great effect on improving the catalytic activity of $FeMoO_4$ nanomaterials.[79] In serum and urinalysis, Raman spectroscopy (SERS) has been shown to have practical advantages over IR absorption spectroscopy,[80] which can be enhanced by nanoparticle surface plasmon resonance (SPR).[81] Table 1 summarizes the applications of nanomaterials in biosensors (Figure 3).

Determination of Oxalate Content in Urine

Some scholars have proposed to use nanoparticle tracking analysis (NTA) to detect human urine nanocrystals-stained with calcium-binding fluorophore Fluo-4AM. After staining, NTA can be used to detect and quantify calcium-containing nanocrystals smaller than 1μm.[8] Oxalic acid plays an important role in the metabolic evaluation of urinary calculi, Researchers have reported a three-signal fluorescence strategy based on the ability of oxalic acid to reduce Cu^{2+} to Cu^{+}, and the selective detection of Cu^{2+} and Cu^{+} by pyrophosphate-cerium coordination polymer network (PPi-Ce CPNs), cadmium telluride quantum dots (CdTe QDs) and N-methyl mesoporous porphyrin (NMM). CdTe QD_S will agglomerate upon Cu^{2+} addition and CuTe aggregates will be formed upon Cu^{+} addition. This structural change indicates that the cation exchange reaction between Cu^{+} and QD_S is more significant than that between Cu^{2+} and QD_S, and that Cu^{+} has a strong ability to destroy the quantum dot structure. Cu^{+} quenched the fluorescence of QD_S, and the signal intensity decreased significantly with the increase of Cu^{+} concentration in the concentration range of 1μM to 600μM, which was more obvious than that caused by Cu^{2+}.[90] The assay has a detection range of 1nm to 100nm with a detection time of 6 minutes. It can be observed that the color change in the solution reflects the oxalate content.[83] A PD-AES based on Hg^{2+} regulation detects oxalate content. This system has successfully achieved oxalate detection at 0.1–10μm with LOD as low as 40nm. Miniaturized plasma AES has the advantages of low cost, low power consumption, small size, and fast analysis speed.[82] This method has been successfully

Table 1 Application of Nanomaterials in the Detection of Stone-Related Components in Urine

Method of Detection	Substance to be Tested	Mechanism	Advantages	Reference(s)
Nanoparticle tracking analysis	Calcium containing nanocrystals	Calcium containing nanocrystals smaller than 1μm were detected and quantified using NTA	High sensitivity	[8]
Electrochemical detection	Oxalate salt	Based on oxalic acid, Cu^{2+} can be reduced to Cu^{+}	The detection range is wide and the time is short	[82]
Electrochemical detection	Oxalate salt	A PD-AES based on Hg2+ regulation detects oxalate content	High specificity	[83]
Rapid and sensitive colorimetric method	Oxalate salt	Oxalate inhibited the oxidation of light yellow TMB to blue oxidized TMB through consumption reaction with MnO_2 nanosheets	High sensitivity	[84]
Electrochemical sensing	Oxalate salt	Vanadium disulfide nanoflowers modify glass carbon electrodes to enhance oxalate sensing	High sensitivity and selectivity with very low detection limit	[78]
Fe3O4NPs@rGOS/GCE sensor	Uric acid	Nanoparticle-modified rGO nanosheets showed good electrochemical reduction peaks.	High stability, repeatability and reproducibility	[85]
High performance liquid chromatography method	Cystine, uric acid, oxalic acid and citric acid	The detection optimization was achieved by using a disposable copper coated nanoparticle electrode (Cun-SPE)	High sensitivity	[86]
Detection using gold nanoparticles	Uric acid	After reacting with melamine, uric acid inhibits the aggregation of gold nanoparticles induced by this substance, thereby detecting uric acid based on the change in color and absorbance of the solution	High sensitivity	[87]
Detection was performed using copper nanoparticles	Uric acid	For the cleavage of MSA on the surface of CuNPs, the small Cu particles were further aggregated into large particles with lightning purple, and the content was judged based on the absorbance	Short response time and high material stability	[88]
Detection using graphene-like two-dimensional sheet carbon nitride nanomaterials	Uric acid	Graphene-like two-dimensional sheet carbon nitride nanomaterials synthesized from melamine have unique structures and properties	High accuracy	[89]
Gold nanostar material was used for detection	Uric acid	The surface of the nanomaterials (gold nanostars) enhances the Raman scattering effect and enhances the Raman signal of uric acid in urine.	High accuracy	[81]
Electrochemiluminescence	Citrate	Selective determination of citrate ions using intrinsic micropore-1 nanoparticles/nitrogen-doped carbon quantum dot polymers	High selectivity and high sensitivity	[77]
Fluorescent sensor	Pyrophosphate	An on-off assay for PPi detection was developed using a new BPHA (BPHA: N, N-bis (pyridin-2-methyl) hexanamine) carbon point	It is easy to operate and accurate	[79]

applied to the determination of oxalate in clinical urine samples, and the results are comparable to those of clinical diagnosis. A rapid and sensitive colorimetric method based on 3,3',5,5' -tetramethylbenzidine – manganese dioxide(TMB-MnO_2) nanosheets was used for oxalate detection.[84] As an efficient biomimetic oxidase, MnO_2 nanosheets can catalyze the reaction with TMB and oxalate. MnO_2 nanosheets are mainly composed of manganese (Mn) and oxygen (O) atoms. Manganese atom is an important component of the active site, which can participate in REDOX reactions. There are amino (-NH_2) groups in the molecular structure of TMB, which can interact with the manganese atoms and oxygen atoms on the surface of MnO_2 nanosheets. The light yellow TMB can be oxidized to the blue oxidized TMB catalyzed by bovine serum albumin stabilized

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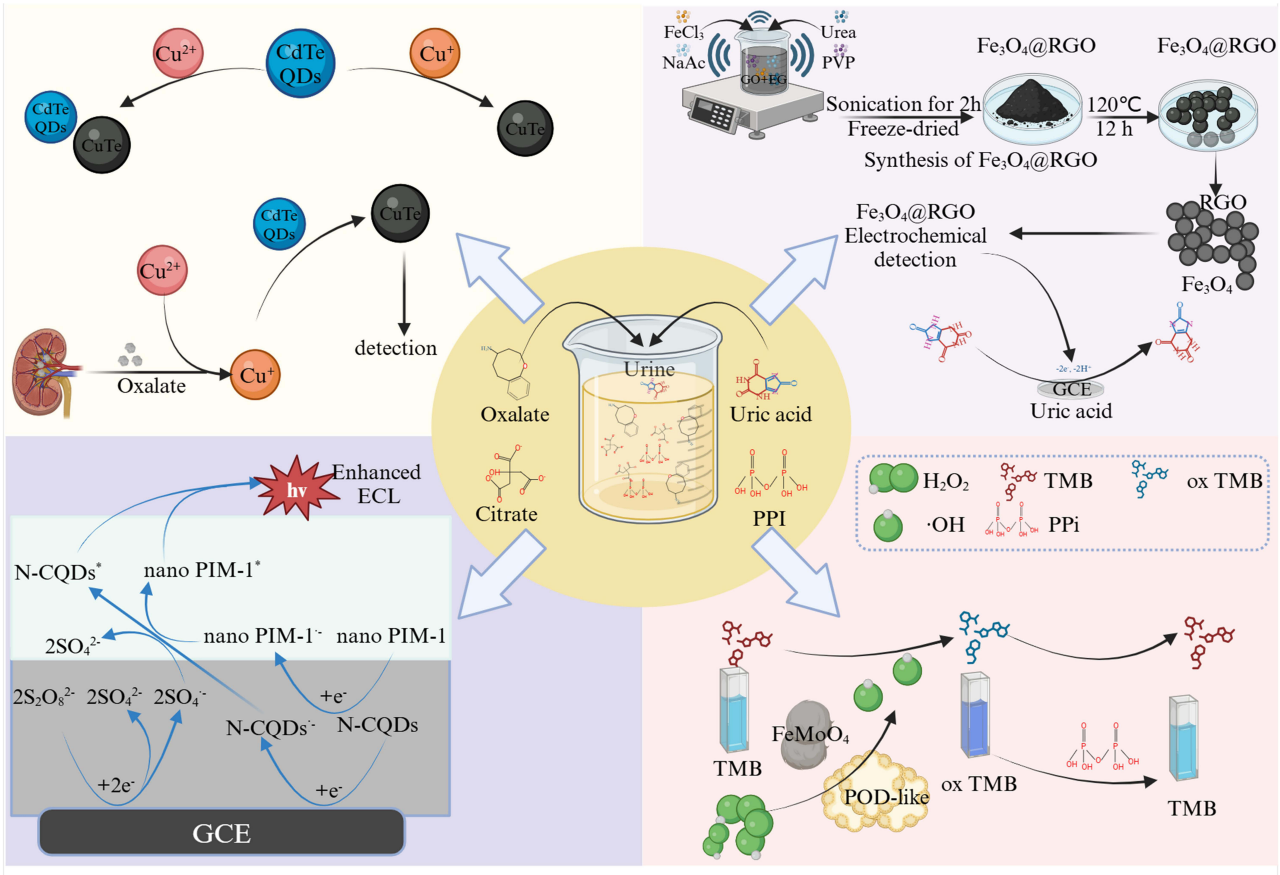

Figure 3 Detection of nanomaterials in kidney stone related ion metabolic processes.

MnO_2 nanosheets, while oxalate can selectively inhibit the reaction by consumption reaction with MnO_2 nanosheets, thus the quantitative detection of oxalate can be achieved. The reliability of the method was effectively verified by testing artificial urine samples, indicating that it has great potential in the bedside application of monitoring and diagnosis of urolithiasis in the population, which can realize early screening and early intervention. One work introduces a novel electrochemical sensing method for oxalate using vanadium disulfide synthesized by hydrothermal synthesis of nanoflowers. The chemical composition and crystal structure of VS_2 nanoflowers play a crucial role in the electrochemical sensing performance.[78] The high crystallinity of VS_2 ensures efficient electron transfer and enhances the conductivity of the modified electrode. The layered structure of VS_2 provides a large surface area and abundant active site for adsorption and oxidation of O oxalate, resulting in increased sensitivity and selectivity. The proposed oxalate sensor exhibits high sensitivity and selectivity over a wide linear detection range from 0.2 to 20um with an extremely low detection limit of 0.188μm.

Determination of Uric Acid Content in Urine

In addition, high concentrations of uric acid in urine can also lead to kidney stones. The RGO nanocomposites modified with super-active iron oxide nanospheres developed in the current research can be used to measure the uric acid concentration in urine and serum samples with high stability, repeatability and reproducibility.[80] Due to the characteristics of crystal structure, some of the iron atoms on the surface of active iron oxide nanospheres are coordination-unsaturated. These coordinated unsaturated iron atoms have high chemical activity, and can form coordination bonds with oxygen atoms and nitrogen atoms in uric acid molecules, so as to realize the adsorption and activation of uric acid, reduce the activation energy of the reaction, and promote the detection reaction. RGO nanosheets inevitably produce some defect vacancies in the preparation process, and the carbon atoms around these defect sites have high activity. Their electronic structure is different from that of the carbon atoms in the intact graphene sheet, which can specifically interact with uric acid molecules, enhance the adsorption ability of uric

acid, and improve the detection sensitivity. Some researchers have used disposable copper coated nanoparticle electrode (Cun-SPE) to promote early diagnosis by detecting creatinine and four urinary stone organic acids (cystine, uric acid, oxalic acid and citric acid).[81] Gold nanoparticles are characterized by high absorption coefficient due to the surface plasmon resonance effect. After reacting with melamine, uric acid was used to inhibit the aggregation of gold nanoparticles induced by the substance, so as to detect uric acid according to the changes in color and absorbance of the solution.[90] An enzyme-free and sensitive method for uric acid field detection was established based on sulfhydryl succinic acid-modified copper nanoparticles, with shorter response time and higher material stability.[79] Graphene-like two-dimensional sheet carbon nitride nanomaterials synthesized from melamine have unique structures and properties. The modified electrode was prepared by compounding it with other substances, and the electrochemical behavior of uric acid was studied by this electrode to realize the quantitative detection of uric acid. For example, oxidized polyimidazole/carbon nitride modified electrodes are prepared, where uric acid will show specific electrochemical signals, and quantitative analysis is performed according to the relationship between these signals and uric acid concentration.[83] The shape of the nanoparticles is key to enhancing the Raman signal.[33] Gold Nano stars typically have a central core and six vertices arranged in 3D.[91] The length of the vertices was 10 nm on average, and the Angle of the vertices was less than 30 degrees. When the gold Nano stars suspension was mixed with urine, The plasma resonance effect can be generated on the surface of gold Nano stars due to the interaction between uric acid molecules and gold Nano stars, and the surface and nearby regions are important active sites. Under photoexcitation, the free electrons in these regions oscillate collectively, generating a strong electromagnetic field that can enhance the Raman signal of uric acid and the gold Nano stars was able to determine the concentration of uric acid in the range of 5–50 μg/mL.[81]

Detection of Citrate Content in Urine

Citrate can bind calcium ions, reduce the concentration of free calcium in urine, alleviate the supersaturation of calcium oxalate, and reduce the risk of stone formation.[92] For the content of citrate in urine, some experiments have pointed out that a sensitive and rapid electrochemiluminescence (ECL) method for conductivity detection has been developed by using intrinsic microporous polymer-1 nanoparticles/nitrogen-doped carbon quantum dots.[77] As the concentration of citrate increased, the ECL signal gradually decreased, which was used to determine the amount of citrate in urine. Based on the above, various components in urine can be analyzed, and the risk of kidney stones is different with the content of components, so as to screen patients.

Determination of Pyrophosphate Content in Urine

Hydroxycalcium phosphate stones account for a large proportion of calcium phosphate stones.[93] Pyrophosphate ($P_2O_7^{4-}$, PPi) is a by-product of the hydrolysis of adenosine triphosphate (ATP) in cells, which plays a crucial role in energy storage, signal transmission and important cellular metabolic processes.[94] More importantly, PPi can act as a natural inhibitor of urinary calculi and can inhibit the formation of calcium-containing crystals in the urinary tract. Therefore, measurement of PPi levels in urine is a measurable factor for urolithiasis prevention. A colorimetric sensing platform for pyrophosphate detection based on Femoo4-H2O2-3,3',5,5' -tetramethylbenzidine (TMB) system was developed for rapid, sensitive and selective detection of PPi in aqueous solution.[79] Iron (Fe) and molybdenum (Mo) ions were the key active site components in $FeMoO_4$ structure. Fe ions have variable valence states (such as Fe^{2+} and Fe^{3+}) and can participate in REDOX reactions. Mo ions can adjust the electronic structure of materials to a certain extent and enhance their catalytic activity. Due to Fe(II) and PPi reactions, the presence of PPi can specifically reduce blue oxidized TMB to colorless TMB, There was a positive correlation between the change in absorbance and PPi concentration.

Application of Nanomaterials Technology in Imaging Diagnosis of Renal Calculi

Imaging Contrast of Renal Stones Enhanced by Nanomaterials

Nanomaterials are ideal structures for biomedical imaging methods. They exhibit one or more contrast imaging capabilities by themselves. At the same time, due to their high specific surface area or easily modified sites, they can provide adsorption, covalent or non-covalent interactions with other contrast agents to produce high-dimensional bimodal

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structures for a variety of biomedical imaging methods. Compared with conventional contrast agents, nanoparticles have better imaging quality[95] and relatively higher safety.[96]

Iodine and gadolinium contrast agents, such as those used in X-ray and magnetic resonance imaging, have a risk of causing kidney fibrosis, but the use of superparamagnetic iron oxide nanoparticles does not, because iron is an essential element in the human body, and it also has an extremely high relaxation rate,[97] Iron atoms with different valence states, such as Fe^{2+} and Fe^{3+}, are important active sites. In MRI imaging, iron atoms in these valence states can interact with hydrogen protons in water molecules, thereby affecting the relaxation time of surrounding protons. and "positive" contrast agents (T1) with bright signals are more suitable for high-resolution imaging. Nanoparticles have unique physicochemical properties such as small size, large surface area, and spectral resonance. Making it an ideal choice for ultrasound imaging. For example, microbubble nanoparticles,[98] as hollow lipid nanoparticles, have unique nonlinear shell properties that generate rich harmonics even at lower pressures, which allows them to provide significant contrast in ultrasound imaging.[99] Through the nonlinear oscillation and pressure dependent response, nanobubbles perform well in ultrasound imaging mode and can effectively suppress tissue scattering (mostly linear scattering) while amplifying their own nonlinear scattering signal, thus clearly displaying the target region. Functional groups such as phosphate groups and carboxyl groups in lipid molecules can be used as active sites. The interaction of charges in functional groups can change the surface charge and stability of microbubble nanoparticles. The change of surface charge during ultrasound imaging will affect the aggregation behavior of microbubble nanoparticles and the interaction with biological tissues, and then affect the imaging effect.

Gold nanoparticles have been shown to enhance contrast in computed tomography (CT) imaging. 2–4 nm AuNPs were captured using a 120 nm polysorbate core with lipid embedding. The formulated particles provide high contrast and high signal-to-noise ratio in CT models and in vivo studies. It is helpful to show the shape and location of kidney stones more clearly.[100] The aforementioned gold Nano stars has multiple arms with sharp corners, which can generate high electric field amplification. In imaging technologies such as surface plasmon resonance enhanced spectroscopy, it can be used as the active site to significantly enhance the interaction with electromagnetic fields, thereby improving the sensitivity and resolution of imaging. Calcium phosphate nanoparticles can interact with calcium components in kidney stones, enhance the imaging effect of kidney stones in X-ray and fluorescence imaging, increase X-ray absorption or fluorescence signal, thereby improving the contrast of imaging, and contributing to the detection and diagnosis of kidney stones.[101] Heavy metal elements with higher atomic numbers and higher absorption coefficients exhibit higher contrast compared to standard iodinated contrast agents.[102] It has been proposed that graphene oxide (GO) is used for imaging diagnosis of kidney, and silver nanoparticles (AgNPs) are composite on the surface of GO to enhance its X-ray absorption, which is used as contrast enhancement agent for computed tomography (CT) imaging. The contrast agent used in positron emission tomography (PET) is a PET imaging probe, and its research and development involve multi-disciplinary cross. DNA nanostructures constructed by the principle of complementary DNA base pairing are known for their simple preparation, controllable structure, and easy biofunctionalization. Some studies have combined DNA nanotechnology with PET imaging technology to explore its application in the diagnosis and treatment of kidney diseases, but the specific research results still need further clinical verification (Table 2).

Application of Nanomaterials Technology in the Treatment of Renal Calculi

Nanoparticles Antagonize the Formation of Renal Calcium Oxalate Stones by Inhibiting Oxidative Stress

Oxidative stress injury of renal epithelial cells plays a crucial role in the formation of renal calcium oxalate stones.[104–106] Oxidative stress can occur through various pathways, increasing the risk of kidney stone formation, and the inflammatory response generated during kidney stone formation further exacerbates oxidative stress, forming a vicious cycle. Antioxidants can antagonise the oxidative stress injury of renal cells caused by hyperoxaluria and inhibit the formation of stones.[90] At present, some nanomaterials with enzymatic and catalytic properties, namely, nanozymes, have been discovered.[107] Nanoenzymes-mediated antioxidant therapy is now considered a promising strategy for the treatment of oxidative stress-mediated inflammation.[108–110]

Table 2 Application of Nanomaterials in Imaging Diagnosis of Kidney Stones

Type of Material	Application of Imaging	Advantages	Safety	Reference(s)
Gold nanoparticles	CT imaging	Contrast and resolution of enhanced CT images.	It is relatively safe, although there may be a slight risk of allergy.	[100]
Iron oxide nanoparticles	Magnetic resonance Imaging	Good magnetic properties, improve MRI signal intensity.	The safety is high, and allergic reactions are occasionally observed.	[97]
Liposome nanomaterials	B ultrasound imaging	It has good biocompatibility and can be used as ultrasound contrast agent.	Generally relatively safe, a few allergic reactions.	[99]
Calcium carbonate nanoparticles	X-ray and fluorescence imaging	It can be used as CT contrast agent to enhance image contrast.	It has good biocompatibility and is generally safe	[101]
Silver nanoparticles	CT imaging	It can improve the quality of CT image.	Further research is needed.	[102]
Graphene oxide nanosheets	Magnetic resonance Imaging	It can be loaded with drugs and contrast media.	The biocompatibility needs to be further studied.	[103]

CeO_2 (cerium dioxide) nanozymes have a unique crystal structure with abundant oxygen vacancies due to their cubic fluorite structure. Ce atom is the core active site, which can present different valence states in the crystal, mainly + 3 and + 4 valence states. This variable valence is one of the key factors for the enzyme-like activity of CeO_2 nanozymes. Different crystal forms, spatial structures and particle sizes of cerium dioxide nanoparticles have different ROS scavenging abilities.[111,112] Because of the change in the valence state of Ce, Deng et al found that the use of porous nanorod CeO_2 nanozymes can catalyze the decomposition of excess free radicals, and scavenging excess ROS is the key to its antioxidant effect. It can inhibit the deposition of calcium oxalate crystals by reducing oxidative stress damage in renal tubular epithelial cells. There were no significant side effects on other organs.[112] Rod-like nanocrystals have a large specific surface area with minimal damage to human hepatocytes, and their antioxidant activity stems from their excellent REDOX properties, with the reduction peak appearing for the first time around 100 °C and the largest total area, and their surface oxygen content is the largest and most easily reducible.

Metal-organic frameworks (MOF) generally refer to a class of crystalline porous materials formed by the self-assembly of inorganic metal centers (metal ions or metal clusters) and bridging organic ligands,[113,114] resulting in the formation of periodic network structures. It is commonly used for in vivo applications due to its outstanding properties such as multiple catalytic centers, wide specific surface area, biodegradability, excellent dispersibility, and biocompatibility.[115] Previous studies have found that MOF-818 is an octahedral structure in which metal ions are an important part of the active site and can act as Lewis acid sites to accept electrons, allowing REDOX reactions to occur, using its antioxidant properties to eliminate excess ROS and alter the oxidative stress environment.[108] The metal nodes decompose superoxide anion radicals and hydrogen peroxide by electron transfer, mimicking the activities of superoxide dismutase (SOD) and catalase (CAT). MOF-818 can transform macrophages from M1 to M2, and inhibit inflammation.[116] Zeng et al showed that MOF-818 could down-regulate the expression levels of adhesion molecules (OPN, CD44) and up-regulate the expression levels of antioxidant markers (CAT, SOD) in renal tissues of rats with kidney stones. At the same time, when the concentration of MOF-818 is 6.25ug/mL, it can restore the vitality of HK-2 cells damaged by oxalate, reduce the proportion of cell death, and achieve a significant protective effect.[108] It is emerging as a promising nanomedicine candidate for effective inhibition of kidney stones. An integrated Nano enzyme with the ability to catalyze a cascade of reactions to eliminate reactive oxygen species (ROS) has been developed. Kinetic analysis shows that this integrated Nano enzyme not only has two spatially separated active sites, which can mimic superoxide dismutase (SOD) and catalase (CAT), but also has a localization effect, which increases the overall reaction rate by

improving the mass transfer efficiency and reducing the transfer time between the catalytic centers. It shows excellent scavenging activity of reactive oxygen species in vivo experiments.[117]

Nanoparticles Can Transform Crystals and Inhibit Nanobacteria

Previous studies have identified a species of nanobacteria from kidney stones, which are thought to be nucleation sites and can further promote the development of calcification.[118] Nanobacteria have unique biomineralization ability and aggregation growth characteristics. Calcification can lead to decreased elasticity of renal tissue and damage to renal tubular epithelial cells.[119] The adhesion of renal tubular epithelial cells to crystals induces the formation of nuclei, which leads to the occurrence of kidney stones.[120] According to existing research work, Calcium oxalate stones are the most common type of kidney stones. There are three different hydrate forms: calcium oxalate monohydrate (COM) crystals, calcium oxalate dihydrate (COD) crystals and calcium oxalate trihydrate (COT) crystals.[121] COM crystals are the most stable, $NanoSe^{o}$ could coordinate with $C_2O_4^{2-}$ in the valence states of C-Se single bond and O-Se single bond, which prevented the formation of CaC_2O_4. At the same time, the formation of spherical COD crystals containing selenium was induced and the growth of COM crystals was inhibited. Since COD crystals are the less thermodynamically stable phase and have a weaker affinity for the cell membrane than COM crystals, the COD crystals will be excreted more easily than COM crystals. In addition, There are related experiments showing that the positive detection rate of nano-bacteria in the medium without selenium nanoparticles was 60%, and the energy dispersive X-ray analysis showed calcium and phosphate peaks. The medium supplemented with 90μmol/L selenium nanoparticles did not observe any nanobacteria, and calcium and other minerals were significantly reduced.[122]

Nanoparticles as an Efficient Carrier for Drug Delivery in the Treatment of Kidney Stones

Nanomaterials as carriers greatly improve the stability and solubility of drug active molecules, promote their transport across biological membranes, and prolong the circulation time in vivo, thereby improving the therapeutic effect.[123,124] It plays an important role in drug delivery system for kidney stones Typically,[125] effective pharmaceutical small molecule compounds are encapsulated in carriers such as synthetic polymers, micelles, and liposomes to form gels, nanoparticles, and microcapsules.[126] As a carrier, therapeutic solid, liquid and gaseous compounds can be encapsulated and effectively delivered to specific targets in vivo.[127] It has been shown that a mixed solution of chelated hexametaphate(HMP)\Fe3O4 nanoparticles and dye is effectively encapsulated by a polylactic acid-polyethylene glycol (PLGA) shell to form uniform-sized microcapsules by a two-drop microfluidic process. Under the action of external magnetic field, it can accurately move to artificial calcium oxalate, and then the PLGA shell breaks under ultrasound irradiation, releasing the internal chelating HMP solution to dissolve the stone.[128] Rutin is a chemical derived from plants with strong antioxidant activity. However, its hydrophobicity and limited bioavailability limit its clinical application. Researchers have developed a biocompatible amphiphilic triblock copolymer, PLGA-PEG-PLGA loaded rutin nanorod. Rutin nanorods (RNS) in the 150–180nm range were developed as polymer nanostructures of rutin, which have higher loading capacity and significantly improved drug bioavailability than conventional delivery systems of rutin. The PLGA chain segment forms a relatively hydrophobic region in the nanorod structure, which is one of the major active sites for rutin loading. Rutin is a flavonoid with some hydrophobicity. During nanorod formation, rutin molecules are attracted between PLGA chain segments, and the hydrophobic regions of PLGA can be encapsulated in rutin by hydrophobic interactions. Rutin nanorods in the range of 100–300nm have good biocompatibility and do not produce toxicity to cells. Higher plasma rutin concentrations have been shown in animal models, and polymer nanostructures can protect rutin from gastro-intestinal factors.[129] In addition, rutin nanorod has a good improvement effect on hyperoxaluria, hypercalciuria and hypomagnesuria.[130] Curcumin is also a polyphenolic compound effective in alleviating oxidative stress, and it can be incorporated into cellulose Nano crystallized with cationic surfactant cetyltrimethylammonium bromide, which can be filtered through the glomerulus and then delivered to renal tubular cells to play a role.[131] For uric acid stones: the development of chitosan-coated magnetic nanoparticles (A-MNPs) loaded with allopurinol has become an effective method for the management of hyperuricemic kidney stones[132] and has achieved good results in preclinical studies. The

developed magnetic nanoparticles were coated with a hydrophilic chitosan polymer to protect the nanoparticles from early clearance by the body's immune system. In vivo studies have shown that the duration of drug release is significantly prolonged and availability is greatly improved[133] (Figure 4).

Nanoparticles Reduce the Residual Rate of Surgical Stones

Ureteroscopic laser lithotripsy is currently a common means of treating kidney stones by using a laser to break the stone into smaller pieces and then removing the pieces or allowing them to pass through. However, according to the existing reports, the stone-free rate of the ureteroscopic approach is only 60–75%,[134] and the residual fragments will lead to the recurrence of clinical symptoms, leaving a hidden danger for the formation of larger stone lesions. The magnetic system currently used for whole kidney stone extraction can significantly improve the efficiency of stone debris removal. Magnetic nanoparticles were prepared from iron oxide nanoparticles. Maghematite, magnetite, and gadolinium, which have the unique property of decomposing into oxygen and iron in the body. When iron oxide nanoparticles with a size of 10nm are synthesized, they exhibit superparamagnetism.[135] Superparamagnetic iron oxide nanoparticles could bind to calcium ions on the surface of calcium oxalate kidney stones, and biopolymer (chitosan) could agglomerate nanoparticles on the stone by ion-gelation. They form a hydrogel to magnetize the stone.[136] Under the action of an external magnetic field, the stone fragments are attracted and trapped. The carbon (fullerene, nanotubes and graphene) and gold (nanorod and nanorod) based photonic nanomaterials with appropriate size, shape, composition and biocompatibility are used to activate the nanomaterials by low intensity (<5w) laser irradiation when the photonic nanomaterials and kidney stones are in contact, directly transferring photothermal and photoacoustic energy to the stone, causing photothermal mechanical stress. Resulting in pulverization,[67] allowing residual stones to be excreted through urine.

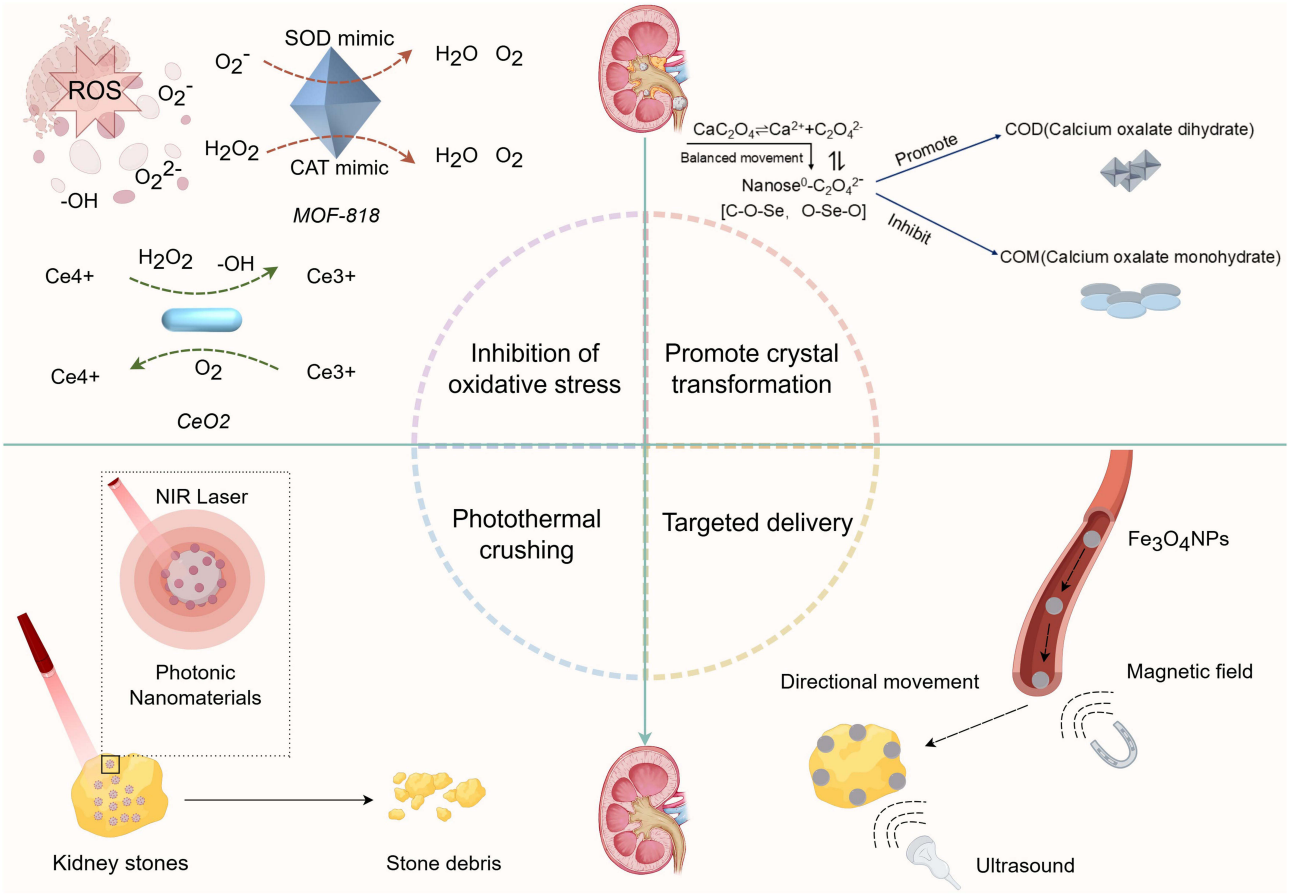

Figure 4 Application of nanomaterials in the treatment of kidney stones.

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Application of Nanomaterials Technology in the Treatment of Renal Calculi Related Complications

Application of Nanoparticles in Urosepsis

Ureteroscopic laser lithotripsy and percutaneous nephrolithotomy often lead to a complication of urosepsis in patients with kidney stones.[137] Sepsis is caused by the invasion of pathogenic microorganisms[138–140] and mainly manifests as life-threatening organ dysfunction with high morbidity and mortality in all regions of the world.[69,141] Without appropriate drug treatment in the short term, the host's immune response may be dysregulated, leading to excessive release of proinflammatory cytokines[142] and death.[143] Bacteria may also be released from the stone surface during the laser lithotripsy procedure. Because there is not enough heat to kill the bacteria attached to the kidney stones when they are crushed by the laser, they are dispersed, and under the pressure of hydronephrosis, bacteria and endotoxin[137] penetrate into the circulation system, which eventually leads to the occurrence of urosepsis. In addition, studies have shown that bacteria also exist in the interior of kidney stones.[144] When residual stone fragments occur during the operation, bacteria can also be widely distributed in the urinary tract and aggravate postoperative infection. The incidence of urosepsis after surgery has been reported to be as high as 7.6% to 16%.[145,146] It will not only bring expensive additional treatment costs to patients, but also endanger the lives of patients, Therefore, early detection, timely diagnosis and intervention of bacteria are very important in its treatment.

In urinary tract infections, Gram-negative bacteria are more common than Gram-positive bacteria. As an important component of the outer membrane of Gram-negative bacteria, endotoxin can shed lipopolysaccharide during growth and infection, which can be used as a biomarker for bacterial detection.[147] Some relevant scholars proposed to use microwaveassisted cysteamine functionalized ZnO nanoparticles (ZNo-Cys) to construct a photoluminescence based biosensor.[148] N-acylhomoserine lactonates (AHLs) are common cell communication signaling molecules in Gram-negative bacteria, which can regulate a variety of physiological processes of bacteria.[149] By detecting AHLs of Gram-negative bacteria, the production of bacterial virulence factors, the synthesis of antibiotics, and the pathogenicity and motility of pathogens can be better determined. Ultrasensitive lipopolysaccharide detection based on adriamycin coupled N-(aminobutyl)-N-(ethylisoluminol)as an electrochemiluminescence indicator and self-assembled tetrahedral DNA dendrimer as a nanocarrier.[150] Existing studies have shown that nanomaterials can often play an antibacterial role through multiple mechanisms.[151–153] This review mainly elucidates that nanomaterials are used as carriers of antibiotics and indirectly complete sterilization according to their unique physical and chemical properties, so as to ultimately improve the condition of sepsis.

Polymyxin B (PMB) itself has a strong adsorption ability and bactericidal effect on lipopolysaccharide. It is very suitable for the treatment of sepsis. However, the dose used limits its widespread use in patients with sepsis. In order to make PMB more safe and reliable for clinical application, we have developed a nanoparticle system, called D-TZP, which can selectively reduce the toxicity of mammalian cells without any effect on the therapeutic activity of PMB. D-TZP consists of iron-complexed tannic acid nanocapeses containing a vitamin D core, coated PMB, and chitosan derivatives that control the interaction of PMB with lipopolysaccharides, bacterial microorganisms, and host cells. D-TZP greatly weakened the cell membrane toxicity caused by PMB, but retained the ability of PMB to inactivate lipopolysaccharides and Gram-negative bacilli.[154] Ilan Klein's group discovered that poly (4, 4-bis (2-ethylhexyl) -cyclopentadiene [2,1-b; 3.4-b] dithiene-2, 6-diyl-azo-2,1, 3-phenylselenadiazole-4, 7-diyl] and FITC-labeled polyethylene glycol (PEG) were used as photothermal agents to excitation the polymer nanoparticles using a light source with a wavelength of 800nm (strongly overlapping with the main absorption peak). The exposure time of 60S can make the nanoparticles produce enough heat to reduce the presence of pathogenic bacteria associated with kidney stones.[68] This study provides a theoretical basis for further exploring the targeted ablation of bacteria adhering to kidney stones by polymer nanoparticles under the stimulation of near-infrared light.

The development of macrophage biomimetic nanoparticles also brings more possibilities for the effective management of patients with sepsis. Nanoparticles made from a macrophage-derived cell membrane wrapped with a polymer core have the same antigenic appearance as the source cell. Using themselves as bait for macrophages to allow nanoparticles to bind tightly and neutralize endotoxin, these macrophage-like nanoparticles also capture proinflammatory

cytokines and inhibit their ability to enhance the sepsis cascade.[69,155] Tetrahedral framework nucleic acid (tFNA) is a new type of three-dimensional nucleic acid nanomaterials.[156] Due to its special physical and chemical properties, it has the advantages of good biocompatibility, stable structure, and editing. The investigators used tFNA as a vector to deliver sirNA-targeted anti-inflammatory therapy to down-regulate TLR2 expression. Experiments have shown that siRNA can specifically reduce the increase of TLR2 induced by LPS and reduce the release of inflammatory factors in experimental sepsis induced by LPS, which provides a good reference for the prevention and treatment of sepsis.[138] Treatment with anti-endotoxin gold nanoclusters significantly prolonged the survival time of mice with LPS-induced sepsis. Ultra-small gold nanoclusters can target lipid A of LPS and inactivate toxicity by compressing its packing density, which may be a potential therapeutic strategy for early prevention of sepsis caused by Gram-negative bacterial infection.[157] In addition, intravenous injection of NO-releasing nanoparticles (NO-NP) can play an anti-inflammatory effect of continuous delivery of exogenous NO, which can improve LPS induced endotoxemia.[158]

Chemostress also plays an important role in the development of sepsis.[159] Many breakthroughs have been made in this field, generally after the initial infection. Hydrogen peroxide (H_2O_2), a potentially toxic reactive oxygen species(ROS),[160] is overproduced by proinflammatory immune cells in the initial stages of sepsis, and they play a dominant role in pathways related to systemic inflammatory immune activation.[161,162] A peroxide scavenger mannose-modified polymeric albumin manganese dioxide (mSPAM) nanoassembly was constructed to catalyze H_2O_2 decomposition. Highly stable mSPAM nanoassemblies inhibited HIF-1α expression by scavenging H_2O_2. Treatment studies in systemic endotoxemia models have shown that mSPAM treatment reduces the inflammatory cytokines TNF-α and IL-6 in the serum, thereby avoiding organ damage caused by inflammatory macrophages, thereby inhibiting the further development of sepsis.[155,163] Interestingly, an integrated cascade Nano enzyme, formulated as Pt@PCN222-Mn, can be used to eliminate excess reactive oxygen species (ROS). The Nano enzyme mimics superoxide dismutase by incorporation of a Mn-[5,10,15,20 tetra-(4-carboxyphenyl) porphyrin]-based metal-organic framework compound, which is capable of converting oxygen radicals to hydrogen peroxide, and by incorporation of Pt nanoparticles, which catalyzes the dismutation of hydrogen peroxide to water and oxygen. Both in vitro and in vivo experimental measurements revealed the synergistic ROS scavenging ability of this integrated cascade of Nano enzymes.[117] Stimulus-response and biomimetic Nano delivery systems are also emerging as advanced biological nanocarriers for enhanced sepsis treatment.[164]

Application of Nanoparticles in Biofilm Prevention and Control

The secreted polymers of bacteria will form a 3D matrix and eventually form a biofilm structure. Bacterial biofilm is a complex microbial community encapsulated by extracellular polymeric substances.[165] They have a certain degree of persistence and refractoriness, showing strong resistance to general antibiotics.[166] Therefore, traditional antibiotic therapy often fails to completely treat biofilm-associated infections.[66,167] Near-infrared activated nanomaterials are widely used in photothermal tumor destruction, energy-gated drug delivery and biofilm eradication.[168–171] Photothermal ablation is a strategy that may eradicate bacteria and destroy renal calculi related biofilms.[172,173] Removal of renal calculi related biofilms and bacteria can effectively reduce the incidence of urosepsis. Nanoparticles capable of absorbing light and rapidly converting it to heat are advantageous for selective thermal destruction, but residual nanoparticles may become potential sites for kidney stone regrowth. Previous studies have shown that polymers can disrupt the formation of calcium oxalate crystals, so the use of polymer nanoparticles to disrupt bacterial biofilms associated with kidney stones becomes an ideal treatment.[174]

Nanoparticles with a size of less than 100nm, such as silver (Ag), nickel (Ni), zinc oxide (ZnO), gold (AU), and copper (Cu) nanoparticles have significant anti-biofilm properties and can exhibit enhanced antimicrobial activity when combined with major drugs used to treat bio membrane-associated infections.[175,176] Development of novel biomimetic tannic acid-based hybrid nanocarriers (HNs) for targeted delivery of ciprofloxacin (CIP-loaded TAH-NPs) against bacterial biofilms. They demonstrated a 3-fold increase in biofilm eradication activity against methicillin-resistant Staphylococcus aureus (MRSA) and a 2-fold increase in biofilm eradication activity against Pseudomonas aeruginosa compared to naked CIP.[177] Nanoparticles have emerged as a superior means of biofilm penetration and treatment.[178] For example, Wu demonstrated a novel anti-biofilm system based on red phosphorus films, which exhibited safe and effective anti-biofilm properties in vitro and in vivo using 808 nm laser at 50°C.[179] They demonstrated a 3-fold increase in biofilm

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Through a large number of literature reviews, it has been found that nanomaterials can strongly interact and react biologically with cell membranes in the treatment of infectious diseases, destroying the integrity of biofilm in a short time.[181] For example, N-trimethylchitosan nanofibers can generate sufficient pressure to cause bacterial lysis and death by relying on electrostatic binding of polycations on the membrane to the negatively charged portion of the bacterial cell wall. Zinc oxide nanoparticles are positively charged and can bind to and destroy negatively charged bacterial cell membranes, leading to leakage of bacterial cell contents and bacterial death.[182] At present, therapeutic nanoparticles, especially polymeric nanoparticles, liposomes,[183] dendrimeric polymers and inorganic nanoparticles, have shown good effects on killing bacteria, and many have been used specifically for local antimicrobial therapy.[184–188] In conclusion, the emergence of nanomaterials technology provides a new strategy for the treatment of sepsis,[189] which greatly improves the prognosis of patients.

Application of Nanoparticles in Accidental Arterial Bleeding Caused by Renal Calculi Surgery

At present, percutaneous nephrolithotomy (PCNL) is the mainstream surgical treatment of kidney stones, and renal puncture is the most critical step of PCNL, because puncture is mainly completed under the assistance of ultrasound, which is not particularly accurate, so it is easy to cause arterial injury and cause bleeding, and in severe cases, embolization is needed. The control of bleeding is extremely sensitive to time, and rapid hemostatic intervention will determine the survival rate of injured patients.[190] In order to reduce the risk of bleeding and other iatrogenic complications in the minimally invasive surgical environment, timely and effective hemostasis is particularly important. Nanomaterials in bioengineering not only focus on rapid and robust efficacy and excellent tissue sealing quality, but also provide better optical visualization for surgeons.[191] When arterial bleeding occurs, a novel bioengineered tantalum loaded nanocomposite hydrogel for gel embolization material (Ta-GEM) can be rapidly delivered using a clinical catheter for immediate hemostasis regardless of coagulation status.[71,192] Ta-GEM preparation can be seen by most clinical imaging methods, including ultrasound, CT, and MRI, and no obvious artifacts are observed. In addition, the operator can retrieve Ta-GEM, resulting in temporary occlusion of the vessel, which can be corrected in a timely way in cases of failed coil embolization. The current experimental results of renal and iliac arteries in animal models show safe and durable hemostatic effects.[193,194] An injectable mesoporous bioactive glass nanoparticle(MBGN)-incorporated biopolymer hydrogel bioadhesive[195] that exhibits strong bonding strength (up to 107.55kPa) at physiological temperatures and can also be removed and reused. The incorporation of MBGN in the biopolymers hydrogel significantly improved the tissue bonding strength compared to the hydrogel adhesive alone, and the bio adhesive exhibited excellent biocompatibility. Avery et al, synthesized a novel gelatin and silicate nanoplatelet hydrogel material with superior biological properties to block blood flow without thrombus formation.[196,197] Nanofibrous materials, such as chitosan nanofibers,[198] can be used for rapid hemostasis at renal artery bleeding sites.[199] It has good biocompatibility and antibacterial property.[85] Nanofiber structure can increase the contact area with bleeding tissue and promote blood coagulation. Synthetic polymer nanofibers such as polylactic acid-co-glycolic acid (PLGA) nanofibers can also be loaded with

hemostatic drugs or growth factors for the treatment of renal artery hemorrhage.[200,201] Iron oxide nanoparticles are superparamagnetic, which can be loaded with hemostatic materials under the guidance of an external magnetic field to accurately localize to the renal artery bleeding site,[202] and achieve hemostasis by promoting platelet aggregation and blood coagulation.

Conclusion and Perspective

This review focuses on the application of nanoparticles in the early urine monitoring, imaging diagnosis, surgical treatment, drug treatment and complication management of kidney stones. The rapid development of nanomaterials provides a new prevention and treatment strategy for kidney diseases, especially kidney stones. Due to its high specificity and high sensitivity, nanoparticles are more widely used in electrochemical biosensors, which can provide early quantitative analysis of compounds in urine and related components involved in the formation of kidney stones, and make a reasonable risk assessment for patients. The current surgical methods for the treatment of kidney stones are still insufficient. The intervention of nanomaterials can greatly improve the efficiency of intraoperative stone removal, reduce the residual stone rate, shorten the operation time, and make the whole process more minimally invasive and avoid further recurrence of kidney stones. Nanoparticles have anti-inflammatory and anti-oxidative stress effects,[203] which can inhibit the occurrence and development of renal calcium oxalate stones. By changing the shape, size, surface charge and composition of nanomaterials, the drug can be better loaded. The drug small molecules modified by nanomaterials have excellent biocompatibility, bioavailability and responsiveness. It can control the release rate of drugs, allow timed release, and long-term drug delivery. It can also achieve targeted drug delivery through molecular recognition, so that more active ingredients can act on the disease site, increase the local effective concentration and therapeutic effect of drugs, and avoid the impact on healthy organs. In terms of complications, nanomaterials also have great advantages, which bring a new direction and choice for the treatment of sepsis. In bacterial infection, nanomaterials can effectively remove biofilms and load antibiotics to kill a variety of drug-resistant bacteria, and participate in hemostasis and repair of arteries as biomaterials for vascular embolization.

However, the long-term side effects of nanoparticles in humans are unknown.[204] The pathophysiological processes involved in the progression of some kidney diseases have not been fully elucidated and require more detailed studies before they can be widely applied. The effectiveness of nanomaterials may change during the translation from laboratory studies to clinical practice. In the laboratory environment, nanomaterials may show good therapeutic effects on cells or animal models. However, in clinical application, individual differences of patients (such as age, gender, underlying diseases, etc.) and the complexity of diseases may affect the actual efficacy of nanomaterials, resulting in less effective than expected.

In order to further better guide the clinical practice, the development of bioactive nanomaterials needs to be further explored and studied in the following aspects: (1) The exploration of chemical mechanism. The study of the chemical mechanism of materials can help researchers better understand the structure-activity relationship of materials and biological functions, thereby providing principled guidance for the design and development of bioactive nanomaterials. (2) broaden the scope of nanomaterials. Future research should focus on investigating the physicochemical properties and biological activities of novel biomaterials. For example, nanomaterials fabricated by 3D printing technology are important biomedical nanomaterials, and exploring their related biological activities will be a promising research direction. (3) to improve the treatment effect of materials. Due to the complexity of biological systems, the therapeutic effects of bioactive nanomaterials are often unsatisfactory. The tissue targeting, biodistribution, biodegradation and immunogenicity of materials should be considered and addressed in our subsequent work.

In conclusion, nanotechnology provides a new approach for the treatment of kidney stones and shows great potential in the diagnosis and treatment of related kidney diseases in the future.

Abbreviations

KSD, Kidney stone disease; ESWL, extracorporeal shock wave lithotripsy; URS, ureteroscopic lithotripsy; PCNL, percutaneous nephrolithotomy; NTA, nanoparticle tracking analysis; NMM, N-methyl mesoporous porphyrin; ECL, electrochemiluminescence; ATP, adenosine triphosphate; BPHA, N, N-bis (pyridine-2-methyl) hexanamine); CT, computed tomography; MRI, magnetic resonance imaging; GO, graphene oxide; PET, positron emission tomography; ROS, reactive oxygen species; MOFs, Metal-organic frameworks; COM, calcium oxalate monohydrate; COD, calcium oxalate

dihydrate; COT, calcium oxalate trihydrate; PLGA, polylactic; acid-polyethylene glycol; RNS, Rutin nanorods; AHLs, N-acylhomoserine lactonates; tFNA, Tetrahedral framework nucleic acid; LPS, lipopolysaccharide; NO-NP, NO-releasing nanoparticles; H2O2, Hydrogen peroxide; mSPAM, A peroxide scavenger mannose-modified polymeric albumin; HNs, hybrid nanocarriers; MRSA, methicillin-resistant Staphylococcus aureus; MBGN, mesoporous bioactive glass nanoparticle; PMB, polymyxin B.

Data Sharing Statement

No new data were collected, and no new ethical approval was required.

Consent for Publication

Informed consent for publication was received from all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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