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Nanoscience Approaches in Treating Urinary Tract Infection with Existing Antibiotic Therapy

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Abstract: A serious worldwide health emergency has been brought on by the growth of multidrug-resistant (MDR) microorganisms, which are difficult to treat with traditional antimicrobial drugs. This emphasises how urgently novel therapeutic approaches are needed to combat antimicrobial drug resistance (ABR). To increase the efficacy of treatment for resistant microorganisms, one such tactic, known as nAbts mixes antimicrobial medications with nanoparticles. This work looks at the development of nano-based treatment systems to treat ABR, specifically urinary tract infections brought on by pathogenic microbes. Important results show that nAbts are more effective than conventional antibiotics. For instance, in vitro research showed that silver nanoparticle-based nAbts decreased bacterial growth in ciprofloxacin-resistant Escherichia coli strains by 98%, as opposed to the 30–40% reduction seen with ciprofloxacin alone. The capacity of the nanoparticles to break down bacterial cell walls, boost medication penetration, and enable targeted delivery—thereby circumventing resistance mechanisms—is responsible for this notable increase in antimicrobial activity. With their capacity to break down bacterial cell walls and promote intracellular drug accumulation, nAbts hold enormous promise for defeating resistance and providing a major breakthrough in the management of multidrug-resistant illnesses. The promise of nAbts to offer safer, more focused, and more successful treatment alternatives for ABR is highlighted in this publication.

Keywords: Nanoscience, Green Nanotechnology, MDR, ABR, Nano-Antibiotics (Nabts), Urinary Tract Infection, Uropathogens, Antibiotic Therapy

1. Introduction

Nano medicine is a rapidly emerging field in science and technology, leveraging the potential of nanotechnology to interconnect with biological molecules at the nanoscale, leading to innovative applications in medicine. A significant advancement in this domain is the development of Nano drugs-nanoparticles designed for targeted medication delivery. By directing active molecules to diseased tissues while minimizing impact on healthy cells, these Nano carriers enhance drug bio distribution and efficacy. In particular, nanotechnology offers the potential for creating biocompatible materials that promote cell growth in regenerative medicine, as well as nanoparticles capable of targeting specific cell types, reducing toxicity, and improving therapeutic outcomes.

Despite the promising advancements of Nano medicine, urinary tract infections (UTIs) caused by multidrug-resistant (MDR) pathogens remain a significant challenge. Traditional antibiotic therapies often fail to effectively treat these infections due to bacterial resistance mechanisms, leading to prolonged infections and complications. This issue underscores the urgent need for novel therapeutic strategies, such as nAbts, which combine nanoparticles with antimicrobial agents to overcome the limitations of conventional antibiotics with unique properties of overcoming resistance mechanism, biofilm disruption, synergistic effects and targeted delivery. The objective of this manuscript is to explore the role of nAbts in addressing the growing challenge of MDR UTIs, with a focus on their ability to improve drug efficacy, enhance bacterial targeting, and reduce the toxicity associated with traditional treatments. By investigating the mechanisms through which nAbts work, this study aims to demonstrate their unique value in providing more effective, targeted therapies for combating UTIs caused by resistant pathogens.

2. Urinary tract infection- An overview

Infections of the urinary tract (UTIs) are brought on by bacteria and other organisms that manage to get past the body's defences. They may have an impact on the tubes that connect the bladder, kidneys, and other organs. The names of UTIs vary depending on the location where they arise. For instance: Cystitis is the term for a bladder infection, Urethritis is an infection of the urethra and Pyelonephritis is the medical term for a kidney infection.

There are two categories for UTIs: simple and complex. Simple UTIs typically just have an impact on the bladder. Infections that are resistant to treatment or have renal effects are referred to as complicated UTIs. The most typical type of urinary tract infections (UTIs) are uncomplicated bladder infections, in accordance to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Reliable Source. Different bacteria can be found on the skin or in the vicinity of the rectum and vagina, according to the Urology Care Foundation (UCF). The bacteria can go to the bladder if they get into the urethra. Some UTIs can disappear without treatment. Some uncomplicated UTIs can clear on their own without treatment, according to a 2022 article from a reliable source, but some people need to see a doctor to get their symptoms under control. If a person experiences UTI symptoms, they should always visit a doctor since they can develop into a kidney infection.

The body often flushes away the bacteria before they get to a person's bladder, according to the NIDDK Trusted Source. A UTI develops when the body is unable to do so in particular circumstances. One of the major prevalent illnesses related to human healthcare is catheter-associated urinary tract infection (CAUTI). Most likely, when catheters are inserted, bacteria enter the body and cause these illnesses. Prolonged usage of urinary catheter is the main prospect for developing catheter-associated UTI (CAUTI). Catheters should only be used at right conditions, and should be removed as soon as when they are no longer required. This infection is brought on by catheters that are ingested. A tube that has been put into a urethra called an indwelling catheter where the bladder is drained, and the urine is collected in a bag. The most significant and noticeable effect of a CAUTI is discomfort or even pain. Your urinary system will itch if you have a UTI. Untreated UTIs can lead to a number of problems, including:

1 A constrained urethra that makes future urination challenging

2 Illnesses that cause kidney damage over time or repeatedly

3 Kidney infections brought on by bacteria that travel through your urethra and bladder

4 Sepsis is a potentially fatal infection of the entire body brought on by bacteria that enter the circulation through the urinary system [1].

Globally and geographically, the frequency of UTI varies based on a number of factors, including population demographics, hygiene habits, antibiotic resistance, healthcare access, and the existence of underlying medical disorders. UTIs are one of the most prevalent bacterial infections in the world, particularly in women, and they contribute significantly to morbidity and the cost of healthcare. A broad summary of UTI occurrence based on regional and worldwide data is provided in table 1 [2].

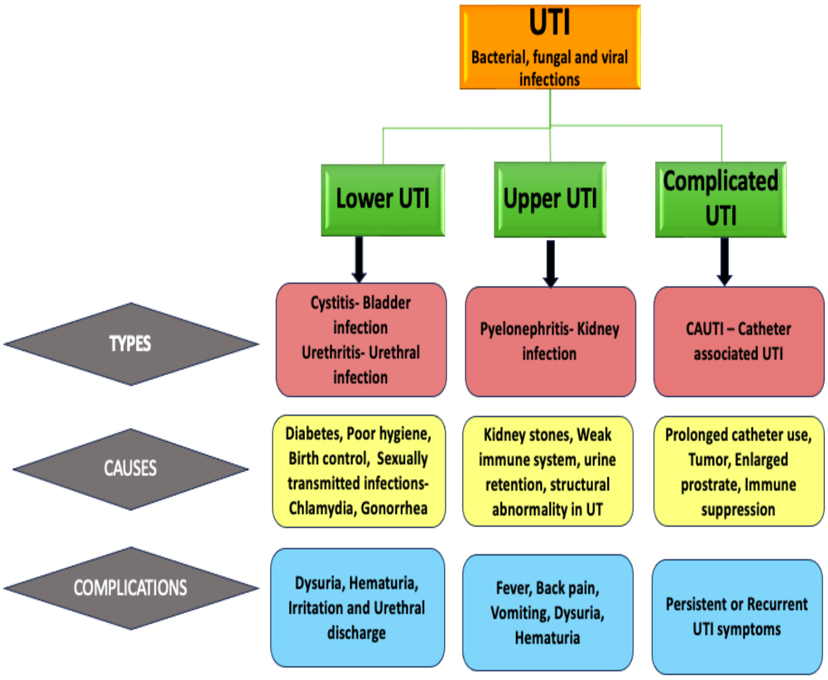

Figure 1. Types, Causes and Risk factors of major UTIs

Table 1. Global and regional UTI prevalence

Region	Prevalence Rate of UTIs
Global	*Annually 150 million cases*
Asia	*3-10% in local population*
Middle East	*Men- 2-4%, Women- 5-10%*
India	*3-8% in local population*
Europe	*8-10 million cases/year*
North America	*10-15% among women*
South America	*20% prevalence in women*
Africa	*4-7% in elderly and children*
Australia	*10-20% among women*

3. Recent advances in nanotechnology and its biomedical applications

The use of nanomedicine as a platform to combat various diseases is growing. The development of nanomedicine has increased patient life expectancy and eliminated diseases that were previously incurable. A nanomedicine platform's benefits include enhancing the pharmacokinetics of medicinal compounds and increasing both their solubility and bioavailability. In addition to offering novel treatments, a nanomedicine platform increases the targetability of diseases. There are several different types of nanomedicines on the market, including protein, lipid, dendrimer, polymeric, and lipid nanoparticles as well as liposomes. Several COVID-19 vaccines to deliver target-specific miRNA use the nanomedicine platform. A number of research communities concentrate on therapeutic approaches employing nanomedicine to treat rare diseases like HIV, HSV, viral infections, cancer, and diabetes. There needs to be a thorough investigation into the drawbacks of nanomedicine platforms, such as the toxicity of some nanomedicines and the long-term side effects. Recent developments in this field, studies have revealed the potential use of nano delivery devices in the delivery of a range of biopharmaceuticals.

Instrumental analysis, process engineering, biochemical assays, quality assurance (i.e., stableness and bioequivalence), in vivo, in vitro, statistical analysis (including AI algorithms), and ethical and social considerations are other components of advanced nanotechnology. Advanced nanotechnology has several uses in the biomedical, environmental, agro-based and automobile fields. The major applications of nanomaterials in various sector is illustrated in fig 2. It encompasses biological information technology, gene sequencing technology, tissue engineering technology, fermentation technology, enzyme engineering, biochip generation, pharmaceutical preparations, and so on. There have been developments in the fields of biomedical products and materials, image processing and diagnostic tools, medical electronics and monitoring devices, fabricated organs, modern therapeutic devices, medical technologies, rehabilitation technologies and products, tissue engineering, and different products based on nanomaterials. Basic components of healthcare work include epidemiological research methodologies, etiological inference, public health emergencies, illness prevention and control, epidemiological statistical overview, statistical studies, and emergency treatment. Furthermore covered are the studies of the human environment, the living environment and good health, the food and health, work settings and health, and the social environment and health.

In 1954, Paul Ehrlich, a physician with a keen interest in immunology and bacteriology, put up the idea of targeted medicine delivery by nanoparticles [3]. In 1973, Professor Peter Paul Speiser with his team conducted the first study on polyacrylic beads for oral drug administration and created NPs for vaccinations and medicine delivery. It was thought that one injection would be enough to trigger the required antibody response since the prolonged drug release mechanism of NPs would continuously stimulate the immune system. Chemical conjugation, physical encapsulation, or adsorption are all possible ways to couple various biological agents with NP kinds. In addition, the manufacture of vaccines and immunisation are two other growing domains. Antiviral applications of NPs in conjunction with anti-drug-resistant bacteria treatments are two more. Nanoparticle-Drug Conjugates (AuNPs), Silver Nanoparticles-Coated Catheters, Ciprofloxacin-Loaded Polymeric Nanoparticles, Magnetic Nanoparticles for Drug Delivery and Pathogen Detection, Quantum Dots for UTI Pathogen Detection and Nanocrystals from Enhanced Levofloxacin are a few specific examples of how nanotechnology is being used to treat UTIs.

3.1 Nanotechnology in Diagnosis

The development of customised medicine, which includes performing diagnostic procedures at the point of care, depends on molecular diagnostics.

The usage of nanoscale particles as tags or labels in diagnostic procedures makes molecular diagnostics more efficient and sensitive because only little amounts of sample material are required. Nano fluidic array chip and protein nano biochips are examples of devices that use nano based biochips and microarrays. Isolating and analysing specific biomolecules, like DNA, is one among the most exciting applications in nanofluidic technology. Systematic biology, customised medicinal drugs, pathogen identification, new drug discovery and pre-clinical research are among the fields in which nanofluidic technology is anticipated to find widespread application.

Figure 2. Unique applications of nanomaterials across various sectors

Some other applications of nanotechnology includes cytogenetics, discovery of biomarkers, stem cell tracking and other molecular diagnostics.

3.2 Nanotechnology in Therapeutics

Nanomedicine may make it easier to provide medications orally if they are now exclusively administered intravenously. Such medications will able to readily pass through the gastrointestinal lining and enter the bloodstream if they are nano encapsulated in a tiny polymer or lipid matrix. Nanoparticles can also efficiently enter damaged cells and help with more accurate diagnosis and treatment. They can be as small as viruses. Oncology has seen the most significant advancements in nanomedicine. Given particular particle sizes and chemical properties, passive targeting of chemotherapeutics to tumour tissues is now a feasible goal for the discovery of Enhanced Permeability-Retention (EPR) effect. Therapeutics are usually larger as, 10 nm to prevention from kidney elimination and those smaller than 150–200 nm to prevent liver and spleen clearance. Nanomedicine research has spanned the gamut of medical specialisations in addition to oncologic uses. Magnetic nanoengineered drugs, quantum dots, nanosuspensions, nanocrystalline drugs, gold nanoparticles, microspheres, liposomes, carbon nanotubes and polymeric nanoparticle designs are just a few of the nanotechnology products being used in medicine today. Nanoparticles actively target the diseased cells to deliver medications at higher concentration while decreasing drug-related effects by preventing or reducing the risk of interaction with normal cells due to their size and special surface features. Figure 3 explains about an enhanced activity of a nanoengineered antibiotic in invading pathogens over a conventional antibiotic under different infectious conditions in the urinary tract.

3.3 Limitations or challenges of adopting nanotechnology in healthcare.

Major challenges based on the usage of NP in healthcare includes; Manufacturing Challenges, Safety and Toxicity Concerns, Limited Understanding of Biological Interactions, Ethical and Public Perception Issues, Complexity of Disease Targeting and Specificity and Challenge of Compatibility with Current Therapies. The smooth integration of nanomedicines into healthcare systems requires cooperation between researchers studying nanotechnology, medical professionals, and regulatory bodies. Furthermore, the safety and efficacy of these novel innovations can be demonstrated primarily by clinical trials and empirical evidence.

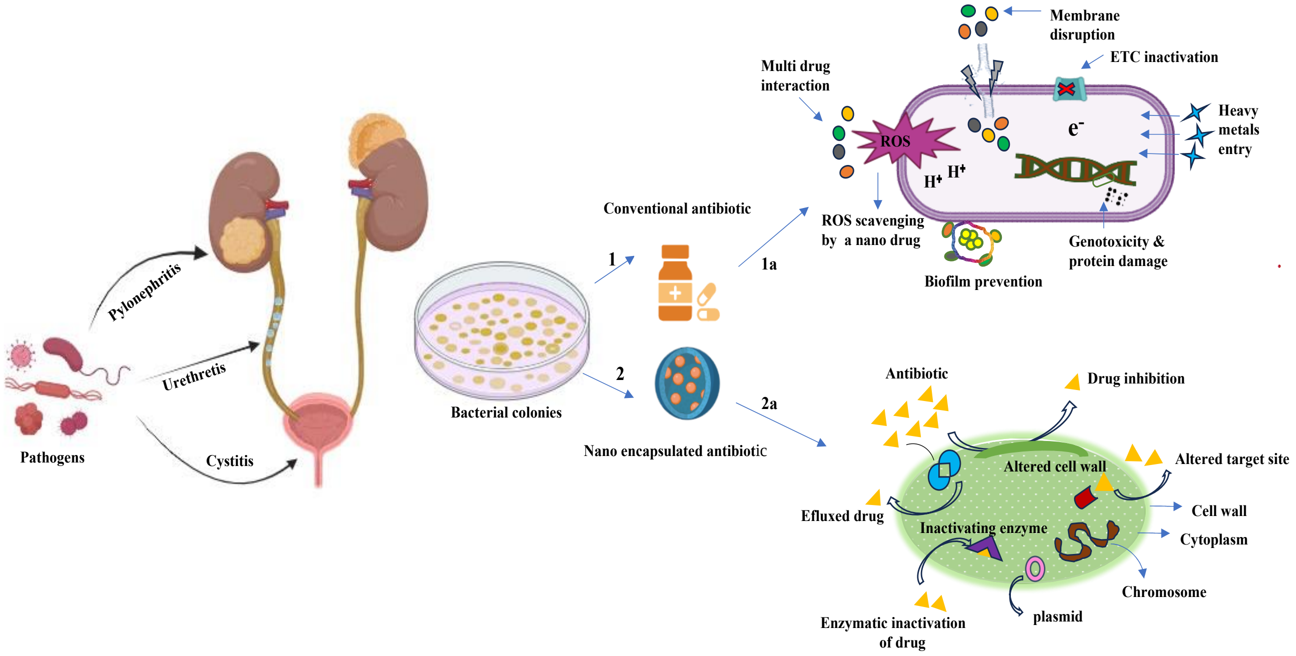

Figure 3. Mechanism of nAbts under various UTI conditions

4. Biosynthesis of nano particles from various sources

Nanoparticles are small, incredibly accurate, and highly mobile particles. In the natural environment, nanoparticles are found in soil, plant biomass, plant extract, ocean spray, and volcanic ash. Existing substances or minerals can naturally be either extremely hazardous or environmentally benign through the bio reduction process.

In the rapidly developing subject of phyto-nanotechnology, isolated biological compounds are used to create, alter, or cover nanoparticles. These particles frequently have intriguing qualities, such as strong biological activity, and can therefore be used in agriculture or medicine. Additionally, phyto-nanotechnology provides fresh and inventive applications for biomass and plant materials that could otherwise be squandered. In recent times synthesis of nanoparticles is highly from plants, micro-organisms (bacteria, fungi, and algae), enzymes and vitamins. For ecologically sensitive applications like agriculture or medicine, green solutions are perfect because they are cost-effective and sustainable [4]. For precise requirements and industrial-scale synthesis, conventional methods prove more effective; yet, as restrictions tighten, their impact on the environment makes them less desirable. Green synthesis techniques for nanoparticles are becoming more and more popular, and they support international sustainability objectives.

5. Green nanotechnology

Green nanotechnology was achieved in response to the demand for an alternate method of producing nanoparticles. The biosynthetic route is considered as secure, biocompatible, environmental friendly green methodology to produce nanomaterial for biomedical applications utilising plants and microorganisms. Plants and other micro-organisms like Fungi, algae, bacteria participates in nano synthesis. Due to the presence of phytocompounds in their extracts, they serves as stabilising as well as reducing agent. Several plant parts involving its roots, leaves, fruits, stems, and seeds have been employed in the synthesis of various nanoparticles [5]. Plants have demonstrated remarkable capability towards heavy metal detoxification and accumulation, which can help address the issue of environmental pollution because even very small concentrations of these heavy metals can be detrimental. Making nanoparticles with plant extract offers some benefits over conventional biological synthesis techniques. The excellent phytochemicals found in many plant parts, including berries, leaves, stems, and their roots, have led to their widespread use in the environmentally friendly creation of nanoparticles which is illustrated in figure 4. The fundamental idea behind green synthesis is that the phytochemicals found in plant parts act as both a natural reductant and a stabiliser for nanoparticles. In addition to being more stable in terms of size and form, NP synthesis using green extracts has a higher yield than those produced by physical and chemical approaches [6]. Numerous researchers have looked into the synthesis of NPs, producing desirable NPs by using bacteria, actinobacteria, mould, yeast, micro-alga and viruses. Microbial cells establish quickly, are easy to maintain, and are equipped to flourish in a range of conditions.

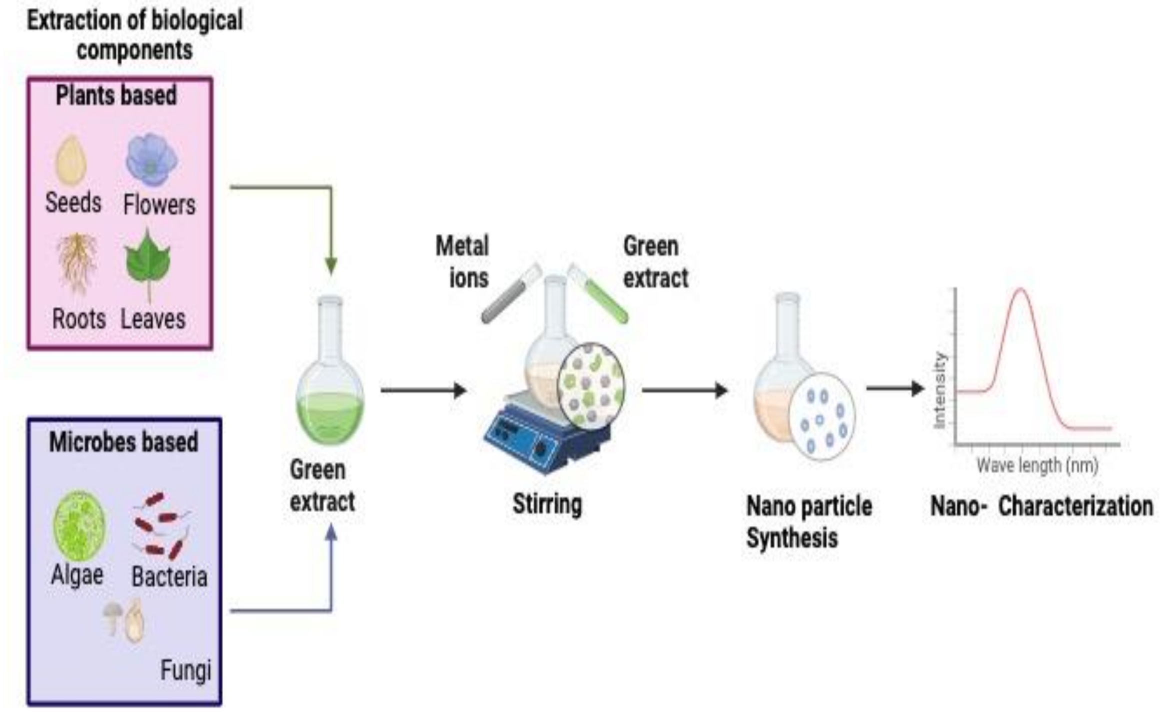

Figure 4. Nanoparticle synthesis from different biological entities

Microalgae and bacteria might generate a variety of special nanomaterials, such as exopolysaccharides, nanocellulose, and nanowires. Microbes exhibiting a steady growth rate can be efficiently grown in artificial settings. Through either extracellular or intracellular avenues, microbes are capable of turning inorganic elements into NPs and can adjust to increasing metal concentrations.

5.1 Bacteria mediated NP synthesis

Bacteria are simple to culture and their genetic codes are easily altered and hence the process of synthesizing nanoparticles are quite feasible. Because bacteria are known to create a variety of inorganic compounds either intra- or extracellularly, they are powerful bio-factories for the generation of metallic nanoparticles such as silver and gold. In a bio-nano factory, a variety of metal NPs, including Ag, Au, Se, Cu and Fe, and metal oxides including silver (Ag_2O), zinc (ZnO), titanium (TiO_2), copper (CuO), manganese (MnO_2), magnesium (MgO) and iron (Fe_2O_3), have been produced [7, 8]. Bacteria are highly capable of producing both intracellular and extracellular metal NPs. It has been proved that extracellular synthesis is more effective and simpler. There have been numerous reports on different bacteria producing metal nanoparticles. *Lactobacillus plantarum* helps in the synthesis process of ZnO nanoparticles. CuO nanoparticles synthesised with the help of *Halomonas elongata* shows antimicrobial activity against *E. coli* and *S. aureus. Bacillus cereus* was used to produce iron oxide nanoparticles, which demonstrated dose-dependent anticancer effects [9]. Alpine *Pseudomonas* produced Pd nanoparticles that were catalytic in de-chlorination processes. Several bacteria, notably *Bacillus licheniformis*, a lactic acid bacteria, can be produced by silver nanoparticles. After a 24-hour incubation period, the nanoparticle's antibacterial activity was seen under the gram-positive bacteria *Staphylococcus aureus* and *Streptococcus pyogenes* as well as the gram-negative bacteria *Escherichia coli, Pseudomonas aeruginosa, and Salmonella*. Additionally, it was shown that it has antifungal efficacy against *Candida albicans*.

5.2 Fungi mediated NP synthesis

Examining fungi's function in nanobiotechnology is seen as essential. Fungi are gaining more attention in research on the biological production of metallic nanoparticles because of their adaptability and capacity to bioaccumulate metals [10]. Because fungi are especially good extracellular enzyme secretors, it is possible to synthesise vast numbers of enzymes [11]. Fungal metallic nanoparticles and nanostructure are produced by the biomimetic mineralisation process with the employment of reducing enzymes, either extracellularly or intracellularly [12, 13]. Metal NPs with various shapes and sizes were produced with the use of fungal biomass/cell-free extract [14]. Despite the use of various fungus species, varied NPs are synthesised in the same experimental criteria. Both metal and its oxides have been synthesised by using some potential strains of fungi which finds a way in biomedical, agricultural and industrial sectors.

The most common NPs to form are quasi-spherical ones, although depending upon the metallic solution along with incubation conditions, other morphology can be attained. By using *F. oxysporum*, spherical silver NPs with a size of 20–50 nm were created [15]. This fungus's ability to reduce metal ions has been linked to shuttle Quinone extracellular processes and NADH-based reductases [16]. In addition to *F. oxysporum*, a large number of different fungal species were utilised to successfully synthesise metal nanoparticles. Significant results were determined from the fungus *Rhizopus oryzae* in producing metallic NPs [17]. It was possible to manipulate the form of gold NPs at RT by using fungi.

NP depends on various kinds and condensation of biomolecules that each fungus species produces and on various incubation conditions, precursor solutions and response time. Though with the use of fungal species, the antibacterial effectiveness of synthesised silver NPs was determined against bacteria and fungal diseases [18, 19]. High antibacterial activity was shown by the nanogold-bioconjugate made with *R. oryzae* against harmful bacteria such as *P. aeruginosa, E. coli, B. subtilis, S. aureus, Salmonella sp., and the yeasts S. cerevisiae and C. albicans* [20]. Metal ions includes some toxic substances, can be removed from ores and water which can be purified, and material synthesis were done by using the microbial process. Fungal production of nanoparticles is an innovative, economical, and environmentally beneficial method. *Fusarium sp.*, which are fungi, are key players in the production of nanomaterials and can be viewed as a kind of nano factory. It has been discovered that fusaria are an adaptable system with the capacity to extracellularly synthesise nanoparticles [21]. Different *Fusaria sp*. can synthesise nanoparticles that are useful in both agriculture and medicine. A rapidly growing area of study, biomedical application has great promise for advancing human disease detection and care. In nano biomedicine, the scattered nanoparticles are typically used as fluorescent bio markers, medications and gene delivery agents [22, 24].

5.3 Yeast mediated NP synthesis

The ability of yeasts, which are eukaryotic microorganisms, to ferment sugar, which entails producing metal nanoparticles with their reducing enzymes intracellularly or extracellularly, makes them key players in the food industry. The quick growth rate of yeast varieties and the utilisation of some basic nutrients have various benefits in the mass synthesis of metal nanoparticles, and yeast production is straightforward to control in lab settings [25]. Se, Au, CdS, Ag, and Ti nanoparticles are synthesised intracellularly by Saccharomyces *pombe* and *Candida glabrata* and numerous fields of use, including drug administration, in-vivo imaging, biosensors, antibacterial, antifungal, and anticancer characteristics. The size and shape of NP depends on its saline conditions and the utilization of yeast cells [26]. Yeast cells are more advantageous as nano carriers due to its encapsulation mechanism. In the synthesis process the metal ions gets reduced when there is an increase in PH of the yeast cell and thereby the enzyme oxidoreductase gets activated. Based on the redox properties of yeast cells, the metal ions are reduced and hence there will be a strong nucleophilic reaction for the synthesis process [27]. Extracellular synthesis of AgNP were synthesized in the culture medium of 0.025 M silver nitrate solution which indicates that the presence of ATP's and enzyme reductases enhances the synthesis process [28]. When the yeast cells, *Pichia jadinii* are exposed to HAuCl4 gold nanoparticles are produced with a strong inhibitory effect [29]. Recently SeNPs are synthesized from yeast cells intracellularly by raising the levels of sodium selenate in the culture medium [30]. Both extracellular and intracellular synthesis from yeast cells is enabled by centrifugation and lyophilization. In recent days, nanoparticles from yeast strains have found a broader applications in all fields. Due to its strong antibacterial property both silver and selenium are highly preferred as substitution for antibiotics [31]. There is an increase in anti-oxidant property with a minimum amount of sodium selenate (5µg) with *Saccharomyces cerevisiae* [32].

5.4 Algae mediated NP synthesis

Algae are a crucial group of photosynthetic micro-organisms both economically and environmentally. In general they are unicellular/multicellular species that lives in freshwater, marine water, or on the moist surface of rocks [33, 34]. The biosynthesis of nanomaterials from algae extracts is a reliable ecological, straightforward, and affordable process. Different groups of algae, including *Chlorophyceae, Phaeophyceae, Cyanophyceae, and Rhodophyceae*, have been used for the production of metallic NPs [35]. Secondary metabolites that originate from algae have been shown to convert metal precursors to nanoparticles. Synthesis may occur either intracellularly or extracellularly depending on the site of NP production. Numerous biomedical applications, including anti-cancerous, anti-bacterial, anti-fungal, biological remediation, and biosensing properties, have been examined for the algal biosynthesised NPs.

6. Potential techniques and methods in nanoparticle synthesis

Materials that fall between 1-100 nm in size are classified as nanomaterials. A prime example of a recently developed technology is nanotechnology, which offers designed nanomaterials with enormous potential for creating goods with significantly better performance. Nanomaterials' exact composition, size, and shape determine their physical and chemical characteristics. An important theme of nanoscience and nanotechnology is the fabrication of nanomaterials and nanostructures. Only when nanostructured materials with appropriate dimensions, form, morphology, crystal structure, and chemical composition are made available will new physical attributes and uses of nanomaterials be viable. In order to research the unique features and phenomena of nanomaterials and realise their potential utilisation in science and technology, their production and process are the fundamental challenges in nanoscience and nanotechnology. Numerous technical techniques have been investigated for the purpose of creating nanomaterials. The synthesis of nanoparticles are done in two general ways [36].

- Top down
- Bottom up

Top-down techniques are simple and rely on either miniaturising bulk production or removing bulk material to create the structure of choice with in the right attributes. Mechanical milling, laser-induced ablation, plasma sputtering and electro-explosion are examples of top-down techniques. The chemical production of nanoparticles is the primary application of the bottom-up approach. In this case, molecules, atoms, or clusters serve as the smaller building blocks from which nanostructures are constructed. The bottom-up strategy includes the solgel method, wet chemical process, spray conversion, chemical and physical vapour deposition.

7. Etiologic of UTI & Uropathogens

Urinary tract infections are thought to have a well-established and largely consistent microbial aetiology. Underlying host variables that worsen UTI, such as age, obesity, body sugar levels, brain damage, or catheterization, also have an impact on the aetiology of UTI. *E. Coli* is the primary cause under community-based symptomatic UTIs in older women [37]. Enterobacteriaceae are mostly recognised in children with simple UTIs. The most common bacteria linked to diabetes patients are *Enterococcus sp*., class B *streptococci*, and *Klebsiella sp*. *Proteus mirabilis* and *Pseudomonas* are two more prevalent uropathogens. Simple infections account for most cases of UTIs. When patients exhibit anomalies related to function, metabolism, or structure, UTIs are deemed complex. *E coli* accounts for 80% of the causal microorganisms associated with uncomplicated cystitis, while *S.saprophyticus* accounts for 5% - 15% of the infections. Complex UTIs have a more varied and oftentimes polymicrobial aetiology. Urinary blockage, neurological disease-related urine retention, immune suppression, failure of the renal system, kidney transplantation, pregnancy and presence of foreign materials like calculi, indwelling catheters or other drainage devices are considered as complications of a complicated UTI [38]. It is more likely for certain people to get from others. Individuals with diabetes may experience immune system modifications that exacerbate their susceptibility to urine infections. UTIs are common among those who have obstructions in their urinary tract, like kidney stones.

A UTI can also result from a man's enlarged prostate gland obstructing the flow of urine. A UTI is more likely to occur in babies who were born with a urinary tract abnormalities. Sometimes surgery is required to fix the issue.

A UTI is more likely to occur in babies with a urinary tract abnormalities. Sometimes surgery is required to fix the issue. Long-term urinary catheter (CAT) users are highly vulnerable to urinary tract infections (UTIs). It is because the bladder might become infected by bacteria on the catheter. Compared to men, women are more likely to have UTIs. This could be because women's urethras are shorter than men's, which facilitates bacteria's quicker passage into to the bladder. A larger prostate gland can obstruct the flow of urine, which can result in a man getting a UTI. Girls are more likely than males to get UTIs, especially among 4 to 8 years [39]. Both symptomatic and asymptomatic UTIs are possible, however asymptomatic bacteriuria (ASB) is more serious because it doesn't cause any symptoms [40, 41].

Globally, UTIs and their consequences account for approximately 150 million deaths annually [42, 43]. Preventing problems from bacteriuria in pregnant women requires screening for early identification and treatment. It has been observed that between 2 and 41% of pregnant women had bacteriuria overall [44]. *E. coli* was the most frequent microbe implicated in the genesis of ASB and UTI amongst pregnant women (63.2 and 61.6%). Pregnant women in India (7.3%), Bangladesh (10.2%), Nepal (8.7%), and Ethiopia (21.2%) and Nigeria (24.7–45.3%) had higher prevalence of ASB [45, 46]. Approximately 1-3 percent of young women have a UTI. *E. coli* was the most frequent bacteria causing ASB in women [47]. It is the primary cause for ASB in 77% of young American women who are sexually active, 72% of school-aged girls, and 65–84% in pregnant women [48, 49]. Prevalence rate of various uropathogens under different microbial genera is shown in table 2.

7.1 Epidemiology of gram positive bacteria in UTI

Numerous species, such as Gram positive microbes *Staphylococcus saprophyticus*, *Enterococcus faecalis,* and *Streptococcus agalactiae*, are linked to simple UTIs. It is more common to find gram-positive bacteria as UTI causative agents. Gram-positive uropathogens that cause simple UTIs have symptoms that are comparable to those of Gram-negative organisms [51].

Table 2. Prevalence rate of different species of major gram positive, gram negative and fungal genera in causing Urinary Tract Infection [50].

Bacterial type	Microbe	Prevalence rate
Gram +ve	Enterococcus faecalis	5-10 %
	Staphylococcus saprophyticus	1-5 %
	Staphylococcus aureus	1-3 %
	Streptococcus agalactiae	1-3 %
	Streptococcus viridans	<1%
	Mycobacterium tuberculosis	<1%
Gram -ve	Escherichia coli	70-90 %
	Klebsiella pneumoniae	5-15 %
	Proteus mirabilis	5-10 %
	Pseudomonas aeruginosa	1-5 %
	Enterobacter spp.	2-5 %
Fungal	Candida albicans	5-10 %
	Other Candida species	5-10 %

7.1.1 Staphylococcus

Gram-positive bacteria with a yellow pigment called *S*. saprophyticus is responsible for 5% to 20% of UTIs acquired in the community along with 42% of UTIs in women aged 16 to 25 [52]. At any given time, *S. saprophyticus* colonises the rectum, urethra, and cervix in over 40% in young, sexually active women [53]. Males rarely have UTIs from *S. saprophyticus* infections without other aggravating factors, although they have been linked to urethritis and as much as to 17% of prostatitis [54, 55]. The majority of male UTIs brought about by *S. saprophyticus* are seen in the elderly or in institutionalized areas [56]. With S. *saprophyticus,* approximately 40% of individuals suffers with acute pyelonephritis; the symptoms are identical to those associated with *E. coli* in magnitude [57, 58]. Prenatal women and those using urinary catheters are more likely to get *S. aureus* UTIs than *S. saprophyticus* UTIs, which are mostly brought on by community-acquired UTIs [59, 60]. Coagulase-negative as a component of the human skin microbiome, *S. epidermidis* is a significant opportunistic uropathogen, particularly in biofilm-associated urine infections linked to indwelling medical implants [61]. 2.5% of CAUTI are linked to CoNS, which includes *S. epidermidis*, and is a major source of hospital-acquired infections [62].

7.2 Enterococcus

Although *E. faecalis* and *E. faecium* of *Enterococcus* were not the primary cause of most community-acquired UTIs, they together account for 15%-30% in catheter-associated UTIs, they are the third most common cause of UTIs obtained in hospitals [63, 64]. Diabetic individuals have a high risk of UTIs mainly from *Enterococcus spp*., which also account for 13% of ASB among diabetics and 4.9% in non-diabetic persons [65, 66]. Prostatitis, of which *enterococci* cause up to 10% of cases, is another condition for which diabetes is a risk factor [67, 68]. Over time, *E. faecalis*-related UTIs have become more common; currently, the ratio of *E. faecalis* UTIs to *E. faecium* UTIs is 5:1 [69]. CAUTI rarely manifests symptoms, in contrast to rising UTI. Additionally, bladder edema, urothelial injury, dysuria, and urine urgency can result from catheterization alone, even when there is a lack of bacterial infection [70]. Comparing CAUTI linked to Gram-negative bacteria to those linked to Gram-positive species, including enterococci, shows that the latter are more inflammatory as indicated by leukocytes within the urine [71].

7.3 Streptococcus

A usual asymptomatic resident of lower gastrointestinal and female reproductive system, *Streptococcus agalactiae* is often referred to be a group B *Streptococcus* (GBS), to the gram-positive β-hemolytic chain-forming coccus. It is estimated that between 1% and 2% among all monomicrobial UTIs are caused by GBS [72]. In addition to the elderly, pregnant women, diabetics, and people with impaired immune systems are particularly at risk for ASB and UTI brought on by GBS. With over 160,000 cases each year in the US, the prevalence of GBS UTIs is a serious public health concern [73]. According to estimates, there are 4.4 systemic GBS infections for every 100,000 people; urosepsis accounts for 14% of these infections [74]. It has been calculated that as many as 7% of prenatal women exhibit large titer of GBS in their urine, compared to the 1% to 2% [75] estimate for the proportion of GBS associated UTIs in young, non-pregnant populations. According to previous research, infants born to mothers having low-titer GBS bacteriuria are more likely to get GBS disease than babies born to mothers without detectable GBS in their urine. A urine culture for GBS is thought to test positive in 4% of women who tested negative for rectal/vaginal colonisation [76, 77]. GBS-related UTIs are widespread in the elderly and almost ten times more common than GBS neonatal infection. In addition, older adults (~15%) have greater mortality rates of invasive GBS infection than do young infants (4%–6%) [78].

7.2 Epidemiology of gram negative bacteria in UTI

Uro-pathogenic *E. Coli* infestations are a major health concern for humans, with tens of billions of US dollars in societal expenses each year. Recurrence and prolonged infection are brought on by an increasing resistance towards synthetic or natural medicines, which also leads to the formation of novel and more dangerous infections. To combat UPEC infections, there are direct and indirect methods. The various facets of UPEC infection will be taken into account in the continuous quest for novel and more potent antibiotics as well as the identification of natural compounds from plants, fungi, and non-pathogenic bacteria. Bacteria in the IBC (Intracellular bacterial communities) can replicate readily, with up to 10^5 bacteria per cell. These bacteria undergo morphological changes, exit the infected cell, and infect other cells.

7.2.1 Escherichia coli

Highly prevalent causative agent of urinary tract infections in humans is *Escherichia coli* and its resistance against antibiotics is increasing globally. The microbe's virulence factor 1, such as the bacterial capsules, fimbriae, flagella, iron scavenging receptors, lipopolysaccharide (LPS) and toxins that disrupt the host cellular process are responsible for the infection caused by *E. coli*. These factors are also linked to the disruption of the most widely used and well-known antibiotics employed in treating uro-pathogenic *E. coli* (UPEC) infections [79]. UPEC infections cause a considerable increase in antibiotic resistance in UTI patients. Between 70 and 95 percent of infections in the urinary tract are associated with *E. coli.* The majority of identified antibacterial treatments can cause the bacteria to become resistant. Globally it is estimated that 150 million people get UTI each year [80]. Patients in the 20–39 age range are more likely to have UPEC, with a higher number of female patients. The resistance of UPEC isolates to several class of antibiotics used to treat UTIs is highly prevalent. It has been shown that *E. Coli* is more sensitive for imipenem and meropenem. Between 2011 and 2020, ampicillin resistance increased dramatically to 97.1% [81, 82]. The drugs with highest rate of *E. coli* resistance were ampicillin and cotrimoxazole, whereas the rate of cefotaxime resistance grew to 38.8% (2011–2013) to 66.7% (2018–2020). Treating children's UTIs is severely limited by the increase in cephalosporin resistance [83, 84]. With a sensitivity of around 25%, the combined use of amoxicillin with clavulanic acid (Augmentin) produced comparable outcomes. When it comes to *E. Coli* sensitivity, medicines belonging to the carbapenem class, such imipenem and meropenem, ranked second.

7.2.2 Pseudomonas sp

An growing percentage of infections obtained in the contemporary hospital context are caused by *Pseudomonas aeruginosa*. 36 infections occur for every 10,000 hospital discharges, making up 8.5070 from all nosocomial infections. It's doubtful that clinical microbiologists overlooked *P. aeruginosa* because it's so simple to cultivate and identify. Hence, changes in patient susceptibility as well as advancements in the field of life sciences are likely responsible for the notable shift in *P. aeruginosa*' s significance as a nosocomial infection.

The third most frequent infection linked to UTIs acquired by catheter use in hospitals is *P. aeruginosa* [85]. The pathophysiology of *P. aeruginosa* infection has been linked to virulence factors, and strains of *P. aeruginosa* that produce pyochelin or pyoverdin, two virulence determinants were recovered from patients with urinary tract infections [86]. Hemolysin production and renal colonisation are directly correlated, as demonstrated by the significantly higher renal bacterial counts and notable tissue damage observed in uricolates of *P. aeruginosa* compared to low producers. Uro-isolates also produce significant amounts of alginate, siderophores, exoenzymes, and hemolysin. *Pseudomonas aeruginosa* is known for developing biofilms on the surfaces of urinary catheters. The bacterium grows in a series of microcolonies, which eventually combine to form biofilms [87, 88]. The most significant component in *P. aeruginosa* biofilms is alginate, an acetylated polymers from beta-d-mannuronic acids and alpha-l-guluronic acids. Biofilms are actually immune to antimicrobial agents and host defence mechanisms, making them difficult to remove. They also contribute to the pathogenicity in *P. aeruginosa* because they frequently result in recurrent and persistent infections [89, 90].

7.2.3 Proteus sp

Catheter-associated UTI (CAUTIs) are generally polymicrobial infections caused by *Proteus mirabilis*, a rod shaped gram-negative bacteria well known for its swarming motility and high urease activity. *P. mirabilis* is classified as a member of the class Gamma proteobacteria and it has identified as a member of the family *Enterobacteriaceae* (*Enterobacteriales)*. Urolithiasis, the growth of kidney or bladder stones brought on by the alkalinization in urine by an enzyme catalysed urea hydrolysis (urease), may accompany infections. Catheter-associated UTI (CAUTI) are infections of the urinary system caused by the colonization of *proteus spp*. Although it causes infections in eye, gastrointestinal tract and wounds it is most commonly associated with urinary tract infections [91, 92]. The urinary catheter surface becomes rapidly fouled by *P. mirabilis* (PM), an agent that causes catheter biofilm formation. This bacteria can penetrate the epithelial cells of bladder and thereby releases a range of cytotoxins that cause destruction to the epithelium and serious histopathology. 70% instances of bacteria-induced stone growth have been linked to the isolation of Proteus species [93]. The urease activity and catheter encrustation in the mouse model of CAUTI appear to be the main causes of the more severe cystitis that ensues from *P. mirabilis* infection [94]. Particular renal pathology is typically the outcome of *P. mirabilis* infection. Pyelonephritis, reflux in the vesicoureteral tract, bacteriuria, increased infection, and possibly septicemia are all caused by crystals that accumulate in the catheter biofilm and may eventually obstruct the lumen and hence preventing the normal flow of urine and causing complications like painful bladder distension and urinary incontinence [95]. Because the majority of patients having

Blocked catheters had PM infections, and 62% of individuals having crystal catheters suffered from bladder stones, it is generally accepted that the formation in crystalline biofilms supports the likelihood of bladder stones [96].

8. Diagnosis and treatment of UTI

Even while laboratory tests can predict the likelihood of a UTI, a precise diagnosis necessitates thorough assessment of the patient symptoms in addition to the test results. The three most typical signs in UTI's are dysuria, urgency, and frequency. Hematuria, vaginal, suprapubic, and urethral discomfort are other symptoms. It is crucial to remember that generalised symptoms such fevers, vomiting, nausea, flank pain, and upper back pain, can signify that an infection has spread towards the upper part of the urinary tract and shouldn't be treated like a simple UTI. When ruling in a UTI, hematuria was probably the most helpful symptom; when ruling out a UTI, dysuria, the frequency, & urgency constituted the most helpful symptoms [103]. The normal signs of a UTI may not be as diagnostic in older persons. While ageing increases the likelihood of UTIs, older women who do not have UTIs typically have higher levels of less severe symptoms of the urinary tract, like urgency and frequency that might be mistaken for UTIs.

The study discovered a substantial correlation between positive urine cultures and symptoms related to the upper urinary tract, including costovertebral discomfort, rigours, fever, dysuria, frequency, and suprapubic and flank pain. Compared to younger women, older adults may have distinct signs and symptoms. Urgency, frequency, incontinence, and trouble emptying the bladder were the symptoms associated with urine storage that were evident in postmenopausal women, while premenopausal women showed more normal symptoms including dysuria and frequency [104]

Table 3. Effectiveness of Antibiotics with respect to bacterial susceptibility (Antibiotics- a, b, c, d, e, f, g, h, i, j and Antifungal- k, l, m) against Uropathogens (a- fluroquinolones, b- nitrofurans, c- β lactams, d- aminoglycosides, e- oxazolidixones, f- hydroxy quinolines, g- glycopeptides, h- polypeptides, i- sulfonamides, j- carbapenem, k- triazoles, l- polyenes, m- imidazoles).

Pathogens	**Existence rate (%)**	**Antibiotics**	**Sensitivity rate (%)**	**References**
Escherichia coli	63.4	Ciprofloxacin ^{a}	59.1	[97, 98, 99]
		Nitrofurantoin ^{b}	57.6	
		Ceftriaxone ^{c}	50	
Klebsiella pneumoniae	23.2	Ciprofloxacin ^{a}	50	[97, 99]
Proteus mirabilis	17	Amikacin ^{d}	80.3	[97, 99]
		Meropenem ^{j}	73.8	
Pseudomonas aeruginosa	17	Amikacin ^{d}	87.5	[97, 99]
		Imipenem ^{c}	83	
Enterococcus faecalis	14.2	Ampicillin ^{c}	73	[97, 99]
		Linezolid ^{e}		
		Nitroxoline ^{f}		
		Vancomycin ^{g}		
Staphylococcus aureus	3.3	Colistin ^{h}	100	[100]
		Trimethoprim/Sulfamethoxazole ^{i}		
Streptococcus spp.	8	Augmentin ^{c}	85	[100]
		Ampicillin ^{c}		
		Cephalexin ^{c}		
		Penicillin ^{c}		
Candida albicans	Less common	Fluconazole ^{k}	80.9	[101, 102]
		Amphotericin ^{l}	76.9	
		Clotrimazole ^{m}	80.9	

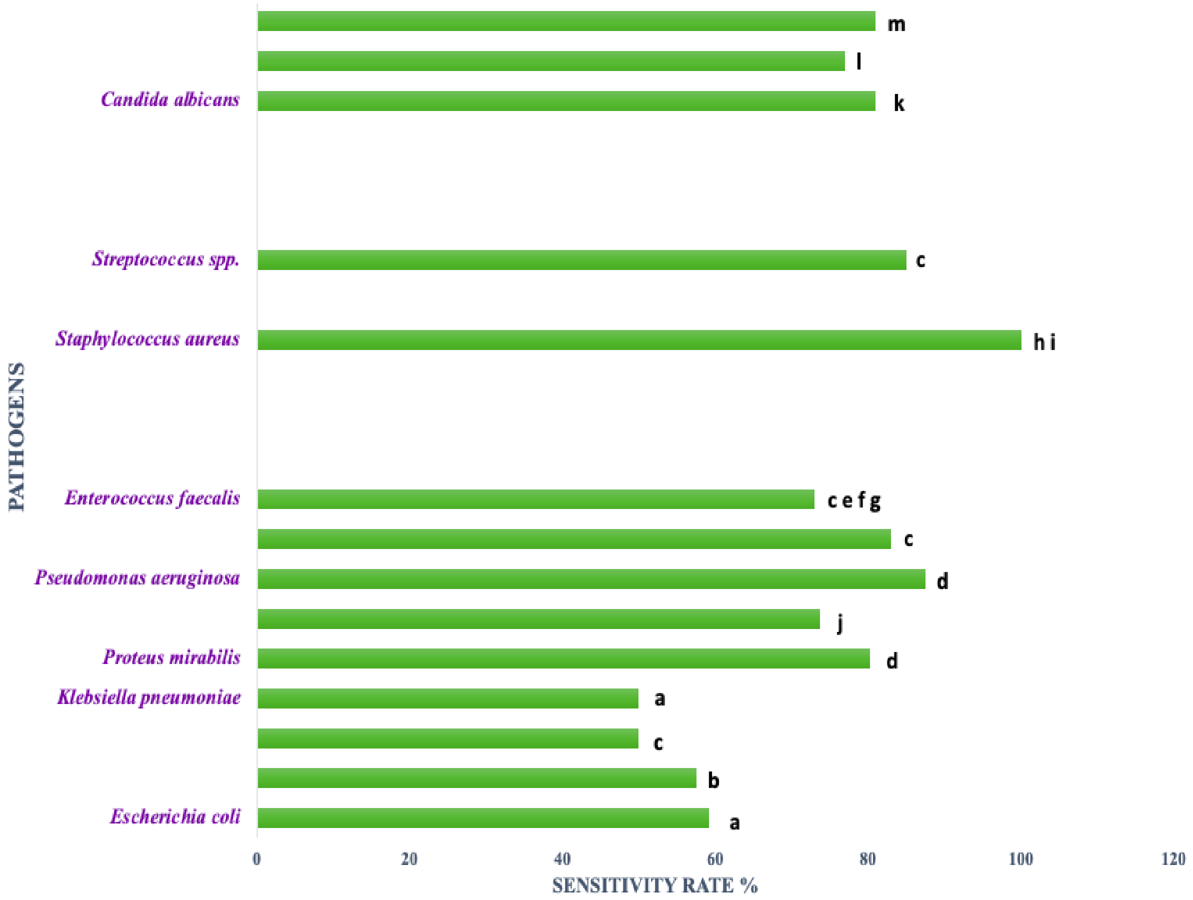

Figure 4. Graphical representation of antibiotics sensitivity rates of different pathogens.(Antibiotics- a, b, c, d, e, f, g, h, i, j and Antifungal- k, l, m), (a- fluroquinolones, b- nitrofurans, c- ・ lactams, d- aminoglycosides, e-oxazolidixones, f- hydroxy quinolines, g- glycopeptides, h- polypeptides, i- sulfonamides, j- carbapenem, k- triazoles, l- polyenes, m- imidazoles).

The likelihood of a urinary tract infection has decreased to 39% in institutionalised women having dysuria and only one clinical characteristic compared to 63% among those with a minimum of one additional symptom. Because the probability in symptomatic UTI is just 1% to 2%, the symptoms and indicators of the illness during pregnancy have not been thoroughly examined [105]. Also, pregnant women do not require treatment for bacteriuria prior to symptom onset. This is because, typically as an effect of ureteric dilatation brought on by increased progesterone, asymptomatic bacteriuria frequently develops into pyelonephritis during pregnancy.

Diagnostic tests of UTI's includes urine analysis (WBC's, nitrites and other variables), urine culture (for bacterial growth), ultrasound (imaging of internal organs), CT (cross section and 3D images), cystoscopy (bladder visualization through cystoscope).

9. Existing Antibiotic Therapy

One major concern for public health is antimicrobial resistance (AMR), which is a component of the problem of bacterial infections. Treating individuals with bacterial infections requires the use of antibacterial medicines. But pathogenic bacteria's developing resistance to antibiotics is limiting their efficiency and raising the risk that antibiotic therapy won't work as intended. The PD (pharmacodynamic) activity of various class of antimicrobials against UTI causing pathogens are listed in Table 3 and the same data is represented in graphical format in figure 4. The need for appropriate treatment of major bacterial infections, particularly in patients receiving intensive care, heightens the urgency of antimicrobial resistance (AMR). Depending on the diagnosis, anti-bacterials must be given in these situations as soon as feasible, ideally within hours [106, 107]. One of the main tenets of modern medicine is the practical application of antibiotics for the treatment of all bacterial diseases. It should be emphasised however, that the original (non-targeted) antibiotic therapy is often required when administering antibiotics, followed by the identification of an etiological microbe and determination of its susceptibility for antibacterial drugs. Much of the therapy with antibiotics, either as a whole or in particular patient subgroups, is incorrect. Antimicrobial drug use was 49.5% of the patient population. Fifty-six percent of patients getting fluoroquinolones and intravenous vancomycin for urinary tract infections or community-acquired pneumonia did not receive enough antibiotics.

A restricted number of chemicals or antibiotic classes used too frequently may lead to an emergence in selective pressure which leads to the development of antimicrobial resistances. Additionally, the prolonged use of specific antibiotic classes increases the chance of resistant bacteria emerging [108]. Extended spectrum β-lactamase (ESBL) producing / β-lactam-resistant gram-negative bacteria, Clostridioides difficile and vancomycin-resistant Enterococcus faecium [109] have all been linked to future infections after cephalosporin [110] use. Quinolone use has been associated with growth in quinolone resistant in gram-negative bacilli, Pseudomonas aeruginosa and infection in methicillin-resistant Staphylococcus aureus [111, 112]. Varying the types of antibiotics prescribed to patients and avoiding those that are linked to a higher risk on resistance induction are two possible ways to lower the likelihood of an antimicrobial resistance resurgence. In nanoscience, sensors and imaging methods facilitate the diagnostic process. These methods include Nano sensors: Instruments with excellent sensitivity and specificity for pathogen identification, Imaging Nanoparticles: Instruments such as quantum dots for in vivo bacterial identification and

Chip-based lab systems: platforms that are smaller for quick diagnostics. Using Nano carriers, nano-antibiotics improve drug delivery and illness treatment efficacy: Drugs are delivered to infection areas by liposomes, dendrimers, and polymeric nanoparticles.

Antimicrobial-containing nanoparticles: Nanoparticles from metals such as gold, silver, and zinc oxide have direct antibacterial properties. Targeted delivery is a sophisticated approach that ensures site-specific release of antibiotics contained in nanoparticles.

Combination Treatments: Using nanoparticles in conjunction with traditional medications to fight resistance and Smart Systems: Drug-releasing responsive nanoparticles that react to infection cues.

10. Nano antibiotics and its application against uropathogens

The term "nano antibiotics" (nAbts) refers to molecules with special physicochemical characteristics that either give them inherent antibacterial action or enable them to act as drug delivery vehicles. It has been discovered that antimicrobial nanoparticle serves as a new alternative for traditional antibiotics. By virtue of their inherent antimicrobial properties, these nAbts are able to eradicate bacteria within diseased cells. Since they are employed to convey medications to the action site, they are also known as nanocarriers. Different metal nanoparticles and ceramic nanoparticles can be combined with traditional antibiotics to target numerous causes of microbial death.

When there is a severe shortage of new medicines, the threat posed by the increasing incidence of antibacterial resistance is constant. nAbts are physicochemical conjugation of antibiotics with tiny particles or artificially synthesised pure molecules of antibiotics in sizes of ≤100 nm with at least one dimension ("Nano on Reflection" 2016) [113]. The efficiency of killing bacteria is determined on the kind of surface charges and their densities, which makes the combination of antibiotics and designed NPs essential. Antibiotic-functionalized negatively charged particles have been the subject of experimentation primarily to enhance the antibacterial capabilities of Nano conjugates. Antibiotic medicines currently in use have made extensive use in both inorganic and organic nAbts (metals, oxides, and carbon-based). A single dose of nAbts can provide the added benefit of a target-specific, regulated prolonged release, which is not possible with most conventional antibiotics. Instead, numerous doses of nAbts are required in a systematic release. To combat antibiotic resistance, several NPs have been functionalized and stabilised using various antibiotic molecule types [114, 115]. While addressing drug-resistant microbes that produce numerous antibacterial mechanisms, NPs have additional functions when compared to the therapeutic effect of a single drug or many medicines together. The greatest threat to all types of antibiotics is posed by multidrug-resistant bacteria. Additional benefits for the efficient and quick death of germs come from the synergistic release of antibiotics from NPs or from the many medicines placed on NPs. The most extensively researched antibiotic currently in use is vancomycin (van), an extremely cross-linked branching of glycopeptide antibiotic, extensively investigated for its in vivo as well as vitro activity in biofilm forming pathogen, in conjunction to the synergy of nanostructured systems [116, 117]. Vancomycin is not efficient against Gram-negative pathogens, while being largely utilised against the Staphylococcus genus [118]. Nonetheless, the conjugates of the NPs and van have a synergistic effect that can effectively eradicate most gram-negative germs and certain multidrug-resistant bacteria. Without releasing itself from the nanoconjugate systems, van prevents gram-positive bacteria from synthesising chemicals from their exterior cell wall which is covalently bonded to the biomaterials. Van attaches to microbial cell wall components with efficiency, attaching more preferentially with D-Ala-D-Ala end moieties found in the peptidoglycan of a bacterium, which inhibits cell development [119]. Several hydrophobic or hydrophilic holes are formed by dendrimers, which, depending on the functional moieties that make up the bioactive terminal surface groups, can encapsulate one or more antibiotics at once. Lipid-coated nAbts can be chemically functionalized by trapping amphiphilic antibiotics concurrently since they have both hydrophilic and hydrophobic cores. Metallic nanoparticles and antibiotic compounds create non-covalent hydrogen bonds. The primary method by which these metal-molecule conjugates kill bacteria is by physically breaking down the cell membrane through surface adhesion and passive diffusion [120]. The most researched and often utilised metals for nano formulations are silver and gold [121, 122, 123]. Metal-oxide nanoparticles (MONPs) are distinguished by their special qualities, which include stability in their net negative surface charge, resistance to swelling, ease of entrapment between hydrophilic and hydrophobic antibacterial agents, ease of functionalization with a wide range of drug molecules and precise engineering towards custom-built particle morphology. Due to some surface interactions such as hydrogen bonding, dipole-dipole attraction, and van der Waal's contact paramagnetic species such as iron oxide NPs are frequently found in the form of MONPs, can offer high efficient drug entrapment. But adding antibiotics (like vancomycin) to them can make them extremely effective antibacterial agents [124]. There is not much literature available on carbon-based nAbts [125, 126]. A carbon nanotube (CNT) and a NGO (nanographene oxides) is stuck inside the cell after physically breaching the membrane. The abts that carry drugs cannot be ejected by the efflux pumps. The superior biocompatibility, bio-uptake capacity, biodegradability, and non-toxicity of Chitosan-based (CS) nAbts make them an attractive option for the functionalization and administration of antibiotics [127]. E. Coli and Staphylococcus sp. can be eliminated by Chitosan treated with penicillin or gentamicin. While 2,6-Di-amino chitosan (2, 6-DAC) exhibits restricted biocompatibility, its hydrophilicity is greatly enhanced when combined with novobiocin. In conjunction with the negative surface charge in the bacterial cell membrane, the net higher positive charges on the surface of CS-nAbts facilitates improved surface binding. In and of themselves, the majority of polymeric NPs have antibacterial properties [128, 129]. Antibiotics with poly (D, L-lactide-co-glycolide)-enabled extended permeability & retention (EPR) primarily target an infection or wound site and several biological components of the bacterial cell, as well as reducing the burden of antibiotic resistance . Clinical investigations have demonstrated the effective reduction of infectious organisms like Chlamydia trachomatis, with PLGA (poly lactic-co-glycolic acid) nAbts with prolonged release and delivery of drugs within chlamydial complex [130, 131]. Mesoporous silica offers a prime illustration of a nanoscale particle that encapsulates antibiotics within porous media. Differential drug release is an exceptional characteristic of mesoporous nano absorptive beads that sets them apart from other kinds. In order to address some of the difficulties associated with functionalized pharmaceuticals containing NPs, many different forms of NPs are principally conceived and subsequently produced [132, 133, 134]. Reducing non-specific release of antibiotic concentration, fostering delivery of multiple antibiotics, preventing toxicological effects, enhancing colloidal dispersion stability, binding through a particular ligand and surfactants (surface-active) category, biodistribution of a drug , improvising localised delivery of functionally active compounds, biodegradability and biocompatibility and so on are some of the things that are included with functionalized nano antibiotics.

10. Antibacterial nano formulations

NPs and antibiotics work together to inhibit the development of bacterial resistance, hence using NPs along with antibiotics is thought to be one way to do this. When used in conjunction with NPs, antibiotics are highly effective against both gram-positive and gram-negative bacteria. Due to their QQ (quorum quenching) characteristics, NPs disrupt virulence components in bacteria, including pigments, digestive enzymes, exopolysaccharides, and toxins. Smaller than 350 nm, NPs are able to penetrate biofilms. The surface charge of NPs affects how they interact with bacteria and biofilms. Positively charged NPs typically pierce biofilms more effectively. Numerous studies have examined the antibiofilm qualities of various metallic and non-metallic NPs. Among these silver [135, 136], gold [137, 138, 139], iron [140] and copper [141] nanoparticles are coupled to antibiotics such as ampicillin, vancomycin, ciprofloxacin and gentamycin which were analysed against both gram +ve and gram -ve isolates. Similarly the efficiency of metal oxide nano-formulations like oxides of zinc and titanium [142] were studied for multi drug resistance against E.coli, S. aureus, Klebsilla spp. and Staplylococcus spp. Based on the previous studies, the MIC (minimum inhibitory concentration) of the nanoparticle- antibiotic system for composite particles shows higher efficacy for anti-microbial resistance for infectious diseases when conjugated with commercial antibiotics with minimum toxicity rates. From the above given references, it is understood that the anti-microbial resistance(AMR) for the nanoparticle coupled antibiotic system shows higher sensitivity rate than existing antibiotics (Amp, Van, CIP, Gen). Among gram negative bacteria Proteus mirabilis shows higher PD activity for Fe3O4-PEG nano composite with gentamicin and with ampicillin E.coli shows high sensitivity for AgNP's. Similarly the gram positive bacteria S. epidermidis shows higher sensitivity rate nano composite- antibiotic system (Fe3O4-PEG- Gen) followed by M. luteus (Amp-AgNP) and E. fecalis (CIP-AuNP). Among metal nano particles K. pneumoniae shows higher activity with gentamicin coupled with copper nano particle.

12. Potential risks and ethical considerations in nAbts development

Although the advancement of nano-antibiotics shows potential, there are a number of possible hazards and ethical issues that should be carefully considered:

Toxicity and Biocompatibility: Due to their distinct physicochemical characteristics, nanoparticles may be immunotoxic, cytotoxic, or genotoxic to people.

They can pass through biological barriers due to their small size, which could have unforeseen consequences; Long-term environmental effects could result from the disruption of microbial populations and other life forms caused by aggregated nanoparticles within soil and water environments; Antibiotic Resistance: Excessive or improper usage of nano-antibiotics may increase bacterial resistance, exacerbating the current antimicrobial resistance (AMR) issue; Absence of Long-Term Studies: One major obstacle to the widespread use of nanoparticles is the lack of knowledge on their long-term effects on the environment and human health. Some of the ethical considerations under nAbts includes,

Equity in Access:

The high expenses of developing and producing nano-antibiotics may prevent low-income and underprivileged groups from having access to them, posing a problem for global health inequity

Ethics of Clinical Trials

Given the ambiguities surrounding the long-term safety of nano-antibiotics, it is imperative that informed consent and openness be guaranteed in trials employing these drugs

Policy and Regulatory Obstacles

Uncertainty surrounds the ethical application of nano-antibiotics due to the lack of standardised standards for assessment, approval, and monitoring. It is necessary to address issues with risk communication, marketing, and labelling

Dual-Use Issues

Biosecurity issues could arise from the possible misuse of nanotechnology, particularly nano-antibiotics; Environmental Justice: The manufacturing and removal of nanoparticles may have an unequal impact on some populations, raising moral questions regarding potential environmental damage in areas that are already at risk.

13. Conclusion

The increasing number of drug-resistant bacteria is rendering conventional antibiotics less effective. In light of these issues, scientific research is looking for a different strategy. In this sense, a medication delivery method based on nanotechnology that may lead to the development of nano antibiotics (nAbts) is viewed as advantageous in the 21st-century technological revolution. As time goes on, the recently developed field of nAbts will require a great deal of attention to produce new therapeutic medications. When it comes to durability, absorption, regulated release, circulation, and distribution, nAbts will outperform conventional antibiotics in a number of ways. Furthermore, nAbts will be affordable, practical, and flexible enough to meet the needs of the world of resistant antibiotics. All of the metallic and metal oxide nanoparticles that were previously discussed showed signs of possible antibiotic synergistic interactions. Their ability to work in concert with conventional antibiotics hasn't been thoroughly studied yet, though. Consequently, research ought to be done to ascertain their function as an adjuvant when paired with commonly prescribed antibiotics. Furthermore, research ought to be conducted on the amalgamation of nanoparticles (NPs) with additional antimicrobial chemicals, like disinfectants and plant essential oils, in order to explore further potential formulations targeting resistant strains of bacteria. A number of nAbts and treatments based on nanotechnology have been approved by the FDA in an attempt to combat issues like antimicrobial resistance (AMR). These include liposomal formulations, nanocrystalline versions of currently available antibiotics, and alternative delivery methods based on nanoparticles. The bioavailability, effectiveness, and targeted distribution of medications are enhanced by these improvements, which also lessen adverse effects. Patients with cystic fibrosis are treated for respiratory infections with Amikacin Liposome Inhalation Suspension (Arikayce®). Combining avibactam with aztreonam stops multidrug-resistant Gram-negative bacteria, such as those that produce metallo-β-lactamases. In addition to investing in research to better understand the efficacy and safety of nanoscale substances used in medicine, the FDA intends to regulate nanotechnology goods within the frameworks now in place. Even though the emergence of nAbts seems promising, there are a number of possible hazards and moral dilemmas. These include issues with safety, toxicity, antibiotic resistance, the environment, regulations, and wider moral considerations [144].

14. Future perspective

The enhanced antibacterial efficacy of nano antibiotics presents a great opportunity for the replacement of conventional antibiotics. A thorough understanding of cellular absorption events is crucial for the creation of more effective nano antibiotics. Future research should focus on clarifying the physicochemical, biological, and pharmaco-toxicological characteristics of nano antibiotics in order to generate a safe and admissible medicines, as of now no FDA-approved products has been made accessible for extensive human usage. In the near future, despite its seeming difficulty, the sequential multistage targeting of metal and metal oxide nanoparticles in conjunction with conventional antibiotics against drug-resistant bacterial planktons may prove to be an effective therapeutic option to counteract antimicrobial resistance and revolutionise the field of nanomedicine. More work will undoubtedly be needed to achieve the goal of more widespread and potent treatments and cures, but the outlook for drug delivery via nanoparticles is encouraging and should eventually produce promising medical products for antibiotic-modified carriers. These seem to be evolutionary improvements over current options rather than revolutionary discoveries.

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Data Availability

The data supporting the findings of this study can be obtained from the corresponding author upon reasonable request.

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