GREEN SYNTHESIZED SILVER NANOPARTICLES AND THEIR BIOMEDICAL APPLICATIONS: A REVIEW

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ABSTRACT

Over the last two decades, scientists have become increasingly interested in metallic nanoparticles due to their unique properties, especially in the biomedical field. Green synthesis of metal nanoparticles is a rapidly growing field in nanotechnology due to its viability, reduced toxicity, ecofriendly nature, and ease of preparation. Plants have long been a centre of attraction in the field of medicine because they are a unique source of a variety of bioactive compounds. Silver has been known for its medicinal properties, especially its antibacterial therapeutic effect. Among other metal nanoparticles, silver nanoparticles have taken a special place since it has made a big impact on medical applications. This review aims to provide a comprehensive understanding of the biomedical qualities of medicinal plants, as well as an overview of their impact on the synthesis of green silver nanoparticles. Various biomedical applications of plant-mediated silver nanoparticles will also be highlighted.

Keywords: Silver nanoparticles; Green synthesis; Biomedical applications; Nanotechnology

INTRODUCTION

substantial Nanotechnology has earned attention in the present century due to its distinctive properties. This makes it an efficient candidate in the multidisciplinary applications field and in numerous 2022). Nanotechnology (Muhammed, comprises the synthesis of nanoparticles (NPs) with various sizes, morphology, and dispersity to be used for their advantage in different ways. It also involves the production of nanostructures with sizes ranging from 1 to 100 nm (Kumar et al., 2018). A nanoparticle (NPs) is a small particle having enhanced properties because of the atomic interaction on its surface, resulting in less coordination than that displayed in bulk materials (Njud, 2022). NPs can be made of metal or non-metal depending on their basic form. Metallic NPs consist of silver, gold, copper, magnetic (cobalt nickel) and semiconducting materials. In contrast, non-metallic nanoparticles are primarily composed of carbon-based materials.

Silver (Ag) is a non-toxic inorganic agent capable of eliminating approximately 650 different types of diseases using microorganisms, therefore, it forms the most essential nanoparticles due to its unique physicochemical properties (Xu*et al.*, 2020). Silver has been described as dynamic because of its ability to exert excellent potential for biological uses, including anti-fungal, antibacterial, anti-viral, wound healing and antiinflammatory properties at low concentrations (HabeebRahuman *et al.*, 2022). Silver nanoparticles (AgNPs) among other nanoparticles have received extensive attention because of their unique properties (Mustapha et al., 2022). Synthesis of AgNps can be achieved either through a top-down or bottom-up approach. The top-down approach involves breaking down a built material into nano-sizes using sophisticated physical such as laser techniques ablation and sputtering. Meanwhile, the bottom-up approach refers to building nanoparticles using smaller entities such as chemical and biological materials. This chemical method requires the use of highly toxic and expensive chemicals, which are difficult to use at a large scale leading to the synthesis of highly toxic nanoparticles (Mohdet al., 2012). However, the biological method which is also referred to as green synthesis was chosen over chemical and physical methods because they are clean, safe. easy prepare, non-toxic. to environmentally- friendly and cost-effective (Christophe and Bilal, 2021). As a result, several biological systems such as bacteria, fungi, yeast, and plant are presently broadly empowered in green synthesis for the creation of AgNPs (Mattew et al., 2021).

AgNPs synthesized with plants are by far the most important biological entity as their comprehensive abundance and lack of pathogenicity offer an advantage over other biological sources. In addition, plant-mediated synthesis is comparably mild with their phytochemical and bioactive contents acting as reducing, capping, and stabilizing agents. Numerous studies have reported the victorious synthesis of AgNPs using different plant species. At their nanoscale size, the AgNPs exhibit significantly different characteristics, as well as improved bioactivity, compared to their bulk counterpart. Green nanoparticles synthesised with plants appear to provide controlled particle size and shape, which is

critical for a wide range of medical benefit of following applications. The synthesis by biological means using plant parts like stems, roots, leaves, bark, flower, peels includes e.t.c non-toxicity. easy reproducibility, and cost-effectiveness. On the other side, the use of plant extract as a reducing agent has also become promising because they contain biomolecules such as carbohydrates, protein, and co-enzymes that possess the capability of reducing metal ions to metal nanoparticles (Alayandeet al., 2021; Salem and Fouda, 2021).

This review is aimed at giving a general overview of the role of plants towards successful synthesis of green AgNPs and to discuss the effective medical potential of green synthesized AgNPs.

Nanoparticles and their classification

European Union (EU) in 2011 defined nanoparticles "as natural or manufactured material which contain particles in an unbound state or as an agglomerate or an aggregate and where 50 percent or more of the particles in the number size distribution, one or more external dimension is in size range 1 to 100 nm". Nano objects requires only one of its characteristics dimension in the size range of 1 to 100 nm to be classified as nanoparticle, even if their other dimensions are outside that range. NPs have an impressively long history. They either exist freely in nature or are artificial. Examples of NPs which exist naturally include organic compounds (such as viruses, bacteria, proteins polysaccharides) inorganic and and compounds dust. (such as natural aluminosilicate and iron oxyhydroxides) which are produced by volcanic eruptions microbial processes, weathering and wildfires (Griffin et al., 2018).

The classification of NPs depends basically on the number of dimensions that lie within the nanometer range (Mishra *et al.*, 2012). Nanoparticles are classified into two main types: organic and inorganic nanoparticles. Organic nanoparticles comprise lipid NPs (micelle, liposome and nanocapsule), dendrimer, hybrid, nanosphere, compact polymeric and nanocapsule and the inorganic NPs; Fullerene, quantum dot, some metallic NPs (silica metal, palladium, silver, lead, Gold, platinum, Ruthenium and Copper (Das *et al.*, 2019).

Organic nanoparticles

Micelles are lipid molecule that arranges themselves spherically in an aqueous solution while micelles form, they respond to the amphipathic nature of fat acids (polymers of lipid), which means that they have both the hydrophobic and the hydrophilic end. The main reason for this spherical formation is because of the hydrophobic interaction, the molecules experience, on exposure to aqueous surrounding separated from water, this lead to the water forming an organised enclosure around the hydrophobic tail (Das et al., 2019). Dendrimers are nano-sized radially symmetric molecules with well-defined, similar and monodispersed structures (Abbasiet al., 2014). Dendrimers are tremendously branched, spherical and multivalent molecules with artificial elastic and several probable usages extruding from catalysis to electronics and drug discharge (Wang et al., 2022). The size of these NPs is effortlessly managed by the of production. Liposomes number are spherical vesicles containing phospholipid bilayers. They are formed from cholesterol and natural phosphides because of their size, hydrophobic and hydrophilic nature. They are encouraging systems for drug delivery with their properties varying significantly with the composition of phosphide's surface charge, the mode of preparation size and (Akbarzardeh*et* al., 2013). The main advantages of liposomes are that they are recyclable, compatible, non-toxic and nonimmunogenic (Das et al., 2019). Nanosphere are particles with a size range between 10 to 200 nm in diameter. They are amorphous and it has been revealed that the hydrophobic areas of these particles are extremely vulnerable to the action of phagocytes (Waliaet al., 2018). A nanocapsule is made up of a shell and a space in which a preferred substance may be placed. Nanocapsules are made from phospholipid

molecules, which are hydrophobic on one end and hydrophilic on the other end and when such molecules are placed in an aqueous environment. they can form capsules spontaneously where the hydrophobic portions are enclosed, protecting them from water contact (Naymihet al., 2019). Fullerenes comprise symmetrical and stable carbon molecules and the most popular fullerene is the inflexible icosahedrons (a polyhedron with 20 faces) with 60 carbon atoms. They are said to be three-dimensional analogues of benzene. Fullerenes are highly strong molecules able to resist high pressures (Amini, 2019). Quantum dots are semiconductors. They are tiny devices that contain droplets of small electrons. They are also referred to as nanometer-sized crystals (Vorobyovaet al., 2019).

Inorganic nanoparticles

Inorganic molecules for example Au (Gold) Ag (silver) PT (platinum) and silica may be employed to generate nanoparticles. Inorganic NPs as shown in Figure 1 below are synthesized through numerous methods. creating an unbending three-dimensional structure (Das et al., 2019). The availability of various types of inorganic NPs and various chemical methods have shown that inorganic NPs can act as a novel system of drug delivery. Several important issues should be considered before using these inorganic NPs in clinical trials. The first important aspect that needs to be considered is the biocompatibility of the inorganic nanosystems. selected Unlike organic NPs, the clinical trials of inorganic NPs are difficult to do due to a lack of data regarding biosafety and toxicity while carrying out these experiments in vivo, and the excretion routes and assessment of toxicity are not well defined. The conventional inorganicbased nanosystem allowed different types of polygenic and monogenic diseases (Sharma and Paul, 2020). The NPs of the inorganic category have three major types: metallic (MNPs), quantum dots (QDs) and metal oxide NPs (MONPs) with MNPs being the focus of this study.

Magnetic inorganic NPs includes gold, copper, silver and palladium types, which have high stability that has been proven in various tumour conditions and they are used as biosensing agents (Vallabani*et al*, 2019). Oxides of silica, zinc, titania and zirconia have high stability and anti-oxidant catalytic actions that make them useful for the medical preparation of implants, bio-imaging and delivery of drugs. Metallic NPs are prepared from metal precursors and they possess a somewhat different property to alkali and noble metals, such as CuNPs and AgNPs. They have a broad absorption band in the visible zone of the electromagnetic spectrum. Metallic NPs are used in various important medical applications such as delivering drugs to areas that are difficult to reach. The particles are also used in the treatment of cancer and other lethal diseases (Xu*et al*, 2022).



Figure 1: Classification of nanoparticles

Synthesis of Nanoparticles

Different methods can be used to synthesize NPs, but these methods are broadly divided into two main classes which are the Bottom-up approach and the Top-down approach as shown in Figure 2. These approaches can further be divided into various classes based on the operation, reaction condition, and adopted protocols.

Bottom-up approach

This approach is also called "building-up synthesis" since it is used in reverse as NPs are formed from nearly simpler substances. Examples of this synthesis as shown in Figure 2, are sedimentation and reduction techniques. It involves Sol-gel, green synthesis, spinning, and biochemical synthesis. Alizarin and titanium isopropoxide precursors were used to synthesize the photoactive composite for photocatalytic degradation of methylene blue. Alizarin was chosen as it gives a strong binding volume with TiO₂ through their axial hydroxyl thermal groups. The anatase formed was confirmed by an X-ray diffraction (XRD) pattern. More recently, the solvent-exchange method is used to attain maximumly sized low-density lipoprotein (LDL) NPs for medical cancer drug delivery. In this process, nuclear ion is the bottom approach followed by growth which is the "up" approach (Abid*et al.*, 2022). In this synthesis, a destructive approach is used, starting from larger molecules, which break down into smaller units which are transformed into suitable NPs. Instances of this synthesis are grinding/milling, Chemical Vapor Decomposition (CVD), Physical Vapor Decomposition (PVD), and other decomposition methods (Abid*et al.*, 2022). This approach is used for coconut shell (CS) NPs synthesis. The milling method was used for this approach and the raw CS powders were lightly milled at different time intervals, with the help of ceramic balls and a popular planetary mill. They showed the outcome of milling time on the general size of the NPs through various characteristics techniques. It was reported as time increases, the NPs crystalline size decreases, as calculated by the Scherer equation. They also realized that with each hour gain, the brownish colour faded away due to the size decrease of the NPs. (Bello *et al.*, 2015).



Figure 2: Typical synthetic method for NPs

Silver Nanoparticles (AgNPs)

Silver is a chemical element with the symbol Ag and atomic number fourth-seven (47). It is a soft, white, lustrous transition metal that reveals the highest electrical conductivity, thermal conductivity, and reflectivity of any metal. The metal is found in the earth's crust in the pure, free element form, as an ally with gold and other metals, and in minerals such as Argentine and chlorargyrite. Silver, in all its forms, has been historically used as an antimicrobial agent by itself or combined with other technologies (Fernandes*et al.*, 2020). This metal has been researched to take advantage of its capacity to obstruct bacterial growth by including it as silver nitrate or silver sulfadiazine in creams and dressing to treat burns and ulcers, in food packaging to prevent contamination, in home appliances such as refrigerators and washing machines, and

several industrial applications (Fernandeset al., 2018).

AgNPs have shown significant dimensions and higher surface (area-to-volume ratio) compared to silver in their bulk form. At this nano-scale, AgNPs show distinctive electrical, optical, and catalytic properties, which has led to the research and production. AgNPs have shown antimicrobial activity in opposition to a variety of transmittable and pathogenic microorganisms, including multidrug-resistant bacteria (Alayandeet al., 2021). The therapeutic applications of AgNPs in terms of antiviral. antifungal. anticancer. and antibacterial properties have also been Presently, demonstrated. AgNPs are commercialized as antimicrobial agents in the pharmaceutical and cosmetic industries and are also used to fight against infections in

various medical implants or bone cement (Ahmad etal., 2020).

Green Synthesis of AgNPs

The green synthesis approach is the most suitable method to overcome the limitations associated with the physical and chemical methods (Akinsipo *et al.*, 2022). This approach is a biogenic, simple, valueeffective, dependable, and environmentalfriendly technique for synthesizing AgNPs. Particular attention has been shown to the formation of AgNPs of defined size and shape. Multiple naturally occurring materials such as plant extract and microorganisms such as fungi, bacteria, and small biomolecules such as vitamins and amino acids are used as another source of reducing and capping agents.



Figure 3: Green synthesis of nanoparticles

It is proposed that the bio-molecules, especially secondary metabolites in those extracts, could reduce the Ag ions (Figure 3). They consist of vitamins, polysaccharides, proteins, amino acids, enzymes, polyphenolics, flavonoids, and other secondary metabolites (Li et al., 2020: Goswamiet al., 2021). Also, the protein found in the plant extracts plays a special role as a reducing agent for Ag⁺ and as a sizecontrolling agent for the preparation of AgNPs. However, this method is associated

with difficulties in terms of growth and culture maintenance. Synthesizing AgNPs using plant extracts offers different advantages in comparison to other green synthesis methods because plants are eco-friendly and easy to handle. Therefore, it offers energy efficiency, low toxicity, high yield, time consciousness, cost-effectiveness, and availability.

Biomedical applications of greensynthesized silver nanoparticles

Due to different properties, AgNPs have been generally used in household utensils, food storage, and the healthcare industry for environmental and biological applications. The present review highlights different biological properties of AgNPs, with emphasis on its and antimicrobial, antidiabetic, anticancer, antioxidant, potential of AgNPs (HabeebRahuman *et al.*, 2022).

Anti-bacterial Activity

AgNPs have a destructive action on the bacterial cell wall by inhibiting the cell respiratory chain and cell nucleic acid (DNA or RNA). AgNPs have been developed as an anti-microbial agent against Multi drug resistant (MDR) bacteria. Due to their large surface area to volume ratio and unique chemical and physical properties, the surface area to volume ratio is high as the particle size decreases (Balachandar et al., 2022). Due to microbial resistance to antibiotics caused by discoveries of anti-bacterial mutation. products are desperately needed. AgNPs have four known anti-bacterial properties, including the microorganisms adhesion to cell membrane; Penetration of AgNPs into cells, which disrupts bio-molecules and intracellular damage; Induces cellular toxicity by generating reactive oxygen species (ROS), which causes oxidative stress in cells; Disruption cell signal of transduction pathways which causes oxidative stress (Alayande et al., 2021).

Bergalet al., (2022) synthesized olive leaf (OL) and green tea leaf (GTL) extract with a green synthesis approach to compare and evaluate characteristic antibacterial the activity of synthesized AgNPs. The formation of AgNPs was observed by the change in colour of the reaction medium from white to dark brown and significantly increases in the basic environment with the temperature antibacterial change. The activity of synthesized AgNPs was compared with that of aqueous OL and GTL by agar well diffusion method. The inhibition zone for E. coli

bacteria increased from 7 to 11 mm in GTLsynthesized AgNPs, and increase from 9 to 10 mm in OL- synthesized AgNPs. Thus, green synthesized AgNPs showed good antibacterial activity at lower concentrations. Another research showed the preparation of AgNPs using different saccharides and potent broadspectrum bactericidal activity against grampositive and gram-negative bacteria. The obvious result of this research was that the prepared AgNPs were active against multibacteria strains resistant such as staphylococcus aureus (Sathiyaseelan et al., 2020).

Antifungal Activity

The dominant group of pathogens in cereal crops is fungi which are responsible for approximately 80% of plant infections. Fusarium fungi are considered to be one of the most toxinogenic microorganisms in the world. The occurrence of these fungi is influenced by several factors, including agronomic practices and climatic conditions that cannot be controlled. For this reason, farmers are looking for alternative replacements for these products to eliminate or reduce plant pathogens (Pandey et al., 2018; Malandrakis et al., 2020; Gorczyca et al., 2021)

Hawaret al., (2022) performed the green synthesis of AgNPs using A. greacorum and its anti-fungal activities were investigated. Scanning Electron Microscopy (SEM) image result indicated the spherical shape of AgNPs with a size range of 22-36 nm. Strong antifungal activities against candida species (C.albicans, C.glabrata, C.parapsilosis, C. tropicales) were observed. It was concluded that synthesized AgNPs from A. graecorum can be used as potential anti-fungal agents for therapeutic various applications. Malvaparviflora was used to biosynthesize silver nanoparticles. The biosynthesized AgNPs were spherical with an average diameter of 50-60nm. The study shows that the M. parviflora is a feasible and eco-friendly method and can be used to explore the development of the fungicide (Al- Otibi et al.,

2021). Dashora et al. (2022) investigated the antifungal activity of AgNPs synthesized with Polyalthialongifolia. UV-vis analysis showed a characteristic peak at 435 nm corresponding to surface plasmonic resonance. The biosynthesized NPs revealed a highly effective potential against plant pathogenic fungi.Beigoliet al. (2021) also used aloe vera plant extracts for antifungal activities. The study shows that *aloe vera*leaves can be used for fabricating and healthcare products supporting cell viability.

Antiviral Activity

Viral infections are a frequent worldwide issue, and it is getting worst almost every day. Therefore, the evolution of antiviral agents is a compulsory request of the day. Viruses, in addition to the coronavirus, grow and multiply rapidly, causing life-threatening illnesses such as HIV, influenza virus, Nipah virus, ebola virus and herpes virus (Rai, 2016). AgNPs are believed to be an effective and potent pharmacological agent with antiviral action. AgNPs play a special role due to their antiviral potential and can inhibit the growth and credibility of viruses AgNPs showed perfect activity against *hepatitis B* virus (HBV) and human immunodeficiency virus (HIV), as concluded by reported research (Verma and Mehashwari, 2019; Terrumieks et al., 2020; Zyildiz et al., 2021). However, the antiviral mechanism of AgNPs remains unknown A reported study related to the antiviral action of AgNPs has proven that they can inhibit the viability of viruses, however, antiviral therapies rely heavily on understanding the mechanism of AgNPs. AgNPs bind with the glycoprotein of the virus and then adhere to the genome and cellular particles. thereby blocking the viral replication process. It is also presented that the use of AgNPs greatly stopped the uplifting of the influenza virus in Madin-Darbycanine kidney cells (mammalian cell lines) and reduced vital titer in lung tissues (Trefry and Wooley, 2013). In a further study, treatment of AgNPs for 24 hours broadly shrunk the concentration of virus, prevalence of infection, and severity of yellow mosaic virus infections (Galdiero *et al.*, 2011).

Antioxidant Potential of AgNPs

Many researchers studied the free radical scavenging activity of plant extract-mediated synthesized silver nanoparticles at various times. NPs formed using plant extracts have enhanced antioxidant activity and it may be to the excellent absorption owing of antioxidants from plant extracts on the surface of nanoparticles. The antioxidant properties of a silver nanosystem obtained from plants are hugely beneficial in the cure of disease. Hence, AgNPs acquired from extracts of plants were reported to have high antioxidant activity (Keshariet al., Gecer 2020). (2021)synthesized **AgNPs**using Salvia green Aeothiopis L. The AgNPs synthesized from S.aethiopis revealed a high antioxidant activity.

Antidiabetic Activity

Nguyen et al. (2022) conducted research on Azadirachitaindica as an excellent and pharmaceutically valuable and phytochemicalenriched traditional medicinal plant. The purpose of the research was to access the ability of A. indica to synthesize AgNPs as well as investigate its anti-diabetic activity. The obtained result revealed that the aqueous kernel extract of A.indica can successfully create the AgNPs which was confirmed on characterization. The obtained results also revealed the number of the functional groups which belong to the pharmaceutically valuable phytochemical, acting as a reducing, capping and stabilizing agent on AgNPs synthesis. Meanwhile, the kernel-synthesized AgNPs showed a reasonable antidiabetic activity (73.5 %) at 100 μ gmL⁻¹ in comparison to the antidiabetic (87.9 %).

Anticancer Activity of AgNPs

Various researchers have reported the role of AgNPs in cancer diagnosis, their cytotoxicity, and their potential as carrier systems for cancer treatment. With their optical properties, high conductivity and small size, AgNPs have demonstrated an essential role in enhancing signals and sensitivity in various biosensing platforms. Furthermore, AgNPs also can be used directly or developed as a drug delivery system for cancer treatment. Many studies investigated in vitro anticancer effects of chemically-synthesized AgNPs on both human and animal cancer cell lines. In contrast, various studies have also shown that chemically synthesized AgNPs displayed toxicity against normal cell lines, although they exhibited significant anticancer effects (Kummara et al., 2016; Boomi et al., 2019). Recently. anticancer the activities of Cuminumcyminum L. (Cumin) seed extract, chemically synthesized silver nanoparticles

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(AgNPs) and biosynthesized silver nanoparticles (Bio-AgNPs) from Cumin seeds on human breast adenocarcinoma cell line (MCF-7) and human breast adenocarcinoma metastatic cell line (AU565) were reported. From the results obtained, Cumin extract showed no inhibitory effects against AU565 cells. On the other hand, AgNPs and Bio-AgNPs displayed considerable anticancer activities on both cell lines (Dinparvar et al., Consequently, current 2020). anticancer research has been devoted to the discovery of novel transition metal compounds. While silver was initially investigated because of its advantageous antimicrobial activity, there has been a recent interest in its anticancer function.

S/N	Plant name/ part	Possible	Application	References
		biomolecule		
		involved		
1.	Acacia nilotica (bark)	Proteins and	Antibacterial	Arya et al., 2019
		phenolic	activity	
		compounds		
2.	Embeliaribes (berry)	Hydroxyl,	Anticancer	Jagtapet al., 2022
		carboxyl, and		
		aliphatic amines		
3.	Acalyphaindica (plant)	Polyphenols, and	Antifungal	Zarowskaet al., 2019.
		alkaloids		
4.	Cassia angustifolia	Phenols, carbonyls,	Antioxidant	Bharathi&Bhuvanesh
	(flowers)	nitro compound,	activity	wari, 2019
5.	Aloe vera (leaf)	Flavonones and	Antibacterial	Buranjeet al., 2021
		terpenoids		
6.	Madhucalongifolia	Hirustrin,	Anticancer	Sarkar <i>et al.</i> , 2018
	(leaf)	bilobalide,	activity against	
		myricitrin, and	breast cancer	
		esculin	cell line	
7.	Tinosporacordifolia	Alkanes, lipids, and	Antioxidant	Selvanet al., 2017
	(leaves)	proteins.	activity	
8.	Phoenix dactyliferia	Alkenes, alcohols,	Antifungal	Oveset al., 2018
	(root hair)	esters, carboxylic	activity	
		acid, esters.		

Table 1: Some biomedical applications of green-synthesized AgNPs

CONCLUSION AND RECOMMENDATION

The review describes silver nanoparticles as interesting metal nanoparticles that possess unique characteristics and numerous therapeutic potential. The review further identifies the different synthetic approaches used in the synthesis of AgNPs while producing detailed information about green synthetic approach. Green biosynthesis of silver nanoparticles mediated plant extracts has numerous advantages over other methods because they are environment-friendly, costeffective and highly suitable for the production of nanoparticles free of toxic contaminants required in bioapplications. In addition, this study highlighted the roles of AgNPs in various biomedical applications. Several reports on the biological activities of AgNPs including antibacterial, antifungal, antiviral, antioxidant, antidiabetic and anticancer were reviewed. From this review, it can be concluded that the green biosynthesized silver nanoparticles using plant extract are more beneficial biologically because plant materials are easy to handle, safe, widely distributed, and readily available. This research can serve as an interesting piece for a basic understanding of nanotechnology and green synthesis of nanoparticles. This research will further place researchers abreast of issues or challenges in their translational to clinical practice and while exploring the prospects that nanomedicine offers in the development of personalized and improved healthcare for mankind.

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