

Nano Warriors: The Role of Cobalt Nanoparticles in Revolutionizing Cancer Therapy

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Abstract: Nanotechnology has emerged as a technology with endless possibilities in numerous fields due to its incomparable magnetic, electric, optical, mechanical, and catalytic properties compared to its bulk properties. This is caused by their noticeably larger surface areas, resulting from the nanomaterial's well-designed structure, which can be accurately controlled by managing synthesis conditions and appropriate functionalization. Metal oxide nanostructures have played a crucial role in the advancement of nanotechnology. Zinc, titanium, iron, cobalt, and copper are the metals most commonly used in the formulation of metal nanoparticles. Furthermore, cobalt functions physiologically as a cofactor for vitamin B12, and due to its distinct size and morphological characteristics, cobalt-based NPs, in general and in particular, are currently generating significant interest. This review article primarily focuses on various synthesis methods for cobalt nanoparticles (CoNPs), including physical, chemical, physicochemical, and biological techniques. Further, potential applications of CoNPs as contrast agents in magnetic resonance imaging. Photothermal therapy, stimuli-responsive drug delivery, and biosensors have been included.

Keywords: NDDS; CoNP synthesis; application of CoNP; theranostic agent; targeted therapy.

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1. Introduction

In the pharmaceutical industry, formulating dosage forms and drug delivery systems that deliver the active pharmaceutical ingredient to the targeted site in the body with high efficiency is a challenging task. Conventional drug development techniques result in the administration of high doses with limited bioavailability, first-pass metabolism, instability, plasma-drug level variability, and repeated dosing, which may also lead to increased side effects [1]. Hence, these limitations of conventional drug delivery systems are addressed by the innovative novel drug delivery system. This nanotechnology aims to reduce off-target effects and improve patient compliance [2]. The history of novel drug delivery systems can be traced back to 1952, with the development of Spansule technology, which introduced sustained-release capsules that released the medicine gradually over a 12-hour period after oral administration. Until the 1980s, commonly used medications for therapy were oral and transdermal medications, which offered continuous 24-hour effects [3]. Lupron Depot, which was developed in 1989, revolutionized drug delivery by enabling longer-acting injectables and implants that last days to months [4,5]. Furthermore, in 2020, lipid nanoparticle formulations

used in COVID-19 vaccines demonstrated the versatility of nanoparticles for vaccine delivery and highlighted the impact of this initiative on medical innovation [6,7]. Hence, the incorporation of nanotechnology into novel drug delivery systems has enabled successful medication administration, thereby advancing this field [8].

A nanoparticle is a small particle whose dimensions are between 10 and 1000 nanometers, and because of this size, it possesses specific chemical and physical properties [9,10]. The term “nanoparticle” is defined as a solid particle that possesses the capability of dissolving, encapsulating, or entrapping drugs in its matrix. This process improves the drug's solubility, stability, bioavailability, and targeting while reducing toxicity and side effects [11]. The American physicist Richard Feynman is credited with founding nanotechnology. His talk, delivered in 1959, "There's Plenty of Room at the Bottom," introduced the concept of nanotechnology. Feynman described how machines, even at the molecular level, can be used to build smaller devices [12]. Nanoparticles gradually gained relevance in the pharmaceutical realm for the development of innovative and effective nanomedicines with high potential for treating various conditions. They have also gained popularity in cancer treatment due to various advantages, such as improved drug delivery, increased solubility, enhanced cellular uptake, sustained release, and targeted drug delivery. For example, polymeric and lipid-based nanoparticles are commonly used for targeted drug delivery, as they can be functionalized with ligands or antibodies that bind specifically to cancer cells [13]. Combination therapy can be achieved using nanocarriers such as gold nanoparticles and dendrimers, which enable the co-delivery of multiple drugs or therapeutic agents, thereby enhancing therapeutic outcomes [14]. Improved imaging is possible with quantum dots and superparamagnetic iron oxide nanoparticles (SPIONs), which provide high-resolution imaging for better tumor localization [15].

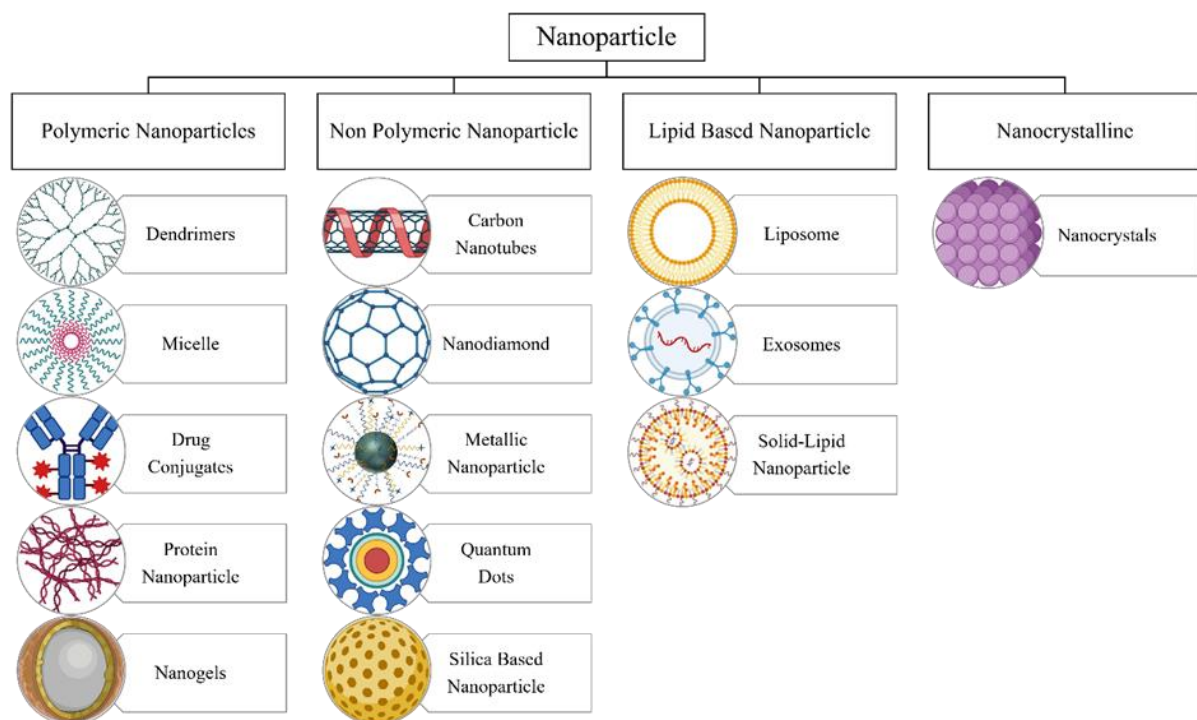


Figure 1. Various types of nanoparticle formulations. Created in BioRender. UIPSR, P. (2025) <https://BioRender.com/s26diqr>.

The biocompatibility and biodegradability of polymeric nanoparticles and liposomes ensure they break down safely in the body, reducing toxicity [16]. Penetration of biological <https://nanobioletters.com/>

barriers, such as the blood-brain barrier, is facilitated by nanocarriers, such as PEGylated nanoparticles [17]. Additionally, silica-based nanoparticles and carbon nanotubes can be engineered with tailored properties, such as size and surface charge, to enhance their interactions with cancer cells [18]. Nanoparticles also protect drugs against degradation in the body, particularly liposomes, which encapsulate drugs and prevent premature breakdown [19]. The versatility of nanotechnology, along with theranostic nanoparticles that combine therapeutic and diagnostic capabilities, reduces adverse effects and improves outcomes in cancer therapy [20,21]. In recent years, scientists have developed various methods for preparing nanoparticles, including metal, non-metal, lipid-based, and polymeric nanoparticles. Some of these commonly developed nanoparticles are shown in Figure 1.

However, metal nanoparticles are currently popular in the realm of drug delivery systems due to their enhanced optical [22], magnetic [23], surface [24], catalytic [25], and electronic attributes [26,27]. These unique properties make them highly effective in various biomedical applications. For example, iron oxide nanoparticles exhibit superparamagnetic behavior, enabling their use in magnetic resonance imaging (MRI) and magnetic drug targeting, in which drugs can be directed specifically to tumor sites using external magnetic fields [28]. Similarly, zinc oxide nanoparticles have demonstrated photocatalytic and photothermal properties, enabling them to act as both therapeutic and diagnostic agents in photodynamic and photothermal cancer therapies [29]. Cobalt oxide nanoparticles, known for their electrocatalytic activity, are being investigated for combination therapy, where they can enhance drug delivery efficiency while also supporting catalytic cancer treatment strategies [30]. Titanium dioxide nanoparticles exhibit high photocatalytic activity, which is exploited in light-activated cancer treatments, such as photodynamic therapy, where they help generate reactive oxygen species that kill cancer cells upon light exposure [31]. These advances in metal oxide nanoparticles were discovered in 1857 by Michael Faraday, an English scientist, while studying the preparation and properties of colloidal suspensions of gold [32]. There has been extensive research on metal nanoparticles for cancer therapy, including the development of platinum nanoparticles for breast cancer treatment and nickel nanoparticles for ovarian cancer [33,34]. Our focus in this review paper is on cobalt nanoparticles, one of many types of metal nanoparticles. This choice is driven by the role of cobalt as a trace element in the human body. Cobalt occurs naturally in tiny levels in the body, mostly in the form of vitamin B12, commonly known as cobalamin. As a result, vitamin B12 functions as a biological reservoir for cobalt. This inherent association emphasizes the relevance of studying cobalt nanoparticles for a variety of biological applications, such as drug transport, imaging, and therapies, which might have consequences for human health and disease management [35,36].

Hence, novel drug delivery systems incorporating nanotechnologies provide new and innovative strategies for delivering the drug in an optimal, predetermined manner. These novel approaches can enhance their efficacy while reducing the side effects. There are many research studies on formulating dosage forms using novel drug delivery systems to enhance their effectiveness. Thus, a wide variety of techniques is explored and used in novel drug delivery systems, and the metal drug delivery system is noteworthy for its unique and intriguing properties. Such a system uses various metal components, such as gold, silver, iron, platinum, and zinc, for drug encapsulation and targeted delivery. This article will go into the details of cobalt-nanoparticle-based drug delivery systems, including various synthesis methods, their advantages, and their applications in the pharmaceutical industry.

2. Cobalt Nanoparticles

Cobalt is a well-known ferromagnetic material used to alloy permanent magnets. Cobalt is one of the most promising metallic nanoparticles and has long been of great importance to researchers due to its wide range of applications in several fields such as gas sensors, lithium-ion batteries, solar selective absorbers, capacitors, field emission materials, energy storage systems, electrochromic thin films, magneto-resistive devices, and catalysis [37–46]. Apart from these, cobalt nanoparticles also have significant importance in the fields of medical science and the pharmaceutical industry through the development of various beneficial innovations [47]. They are used for the development of customizable biosensors [48], organ-on-chip methodologies, medical devices such as orthopaedic implants [49], cardiac stents [50], dental implants [51], surgical instruments [52], pacemakers and implantable defibrillators [53], bone plates and screws [54], and neurological implants [55]. Cobalt nanoparticles are among the most intriguing forms of nanotechnology, offering targeted therapies and synergistic effects to address a variety of issues. In one study, it was reported that citrate-coated cobalt nanoparticles combined with 1 Gy of gamma radiation; the radiation therapeutic efficacy of the combination was increased fivefold, suggesting that cobalt nanoparticles may be used as radiosensitizers in the treatment of cancer. Additionally, it serves as a more effective catalyst for reactions that generate reactive oxygen species, which increases the risk of DNA damage and the death of cancerous cells [56].

2.1. Core of the cobalt nanoparticle.

Cobalt nanoparticles are mainly composed of the core that determines their quality and effectiveness for a given treatment, contributing to their exceptional properties and diverse applications. Hence, it acts as the essential constituent of cobalt nanoparticles. There are different types of cobalt nanoparticle cores, such as cobalt oxide, cobalt nitrate, cobalt chloride, cobalt ferrite, cobalt acetate, and cobalt carbonate. Which cobalt oxide is mostly used in the development of nanoparticles due to its unique properties, such as magnetic properties, catalytic activity, biocompatibility, thermal stability, optoelectronic properties, pH sensitivity, electrical conductivity, photoactivity, and versatility? Cobalt oxide is the new horizon in cancer therapy. It was discovered that cobalt oxide exhibits intriguing optical, magnetic, field-emission, and electrochemical properties, making it appealing for device applications. As a result, enormous effort has been devoted to the production and study of the characteristics of cobalt oxide nanostructures in recent years [57].

The majority of cobalt oxide nanoparticles' characteristics, particularly their catalytic and magnetic ones, rely on their size and shape [58]. Moreover, Cobalt oxide nanoparticles perform better than their bulk counterparts and offer customizable chemical and physical properties [59]. In an oxygen-containing environment, cobalt oxide is thermodynamically stable, offering reliability, robustness, and adaptability across a wide range of technological applications, from energy storage and biological domains to catalysis and sensing [60].

2.2. Coating of cobalt nanoparticles.

While the core of these nanoparticles serves as the foundation for their functionality, the choice of coating material plays a crucial role in determining their stability, biocompatibility, and efficacy as drug delivery systems. One of the key advantages of using coating materials is their ability to improve the stability of nanoparticles, preventing

aggregation and degradation in physiological environments [61]. Coatings also allow the modification of nanoparticle surface properties, such as charge and hydrophilicity, which can affect their interaction with biological molecules and cells. Furthermore, coating materials give stealth properties to the nanoparticles, reduce their recognition and clearance by the immune system, and prolong their circulation time in the bloodstream. In addition, coatings can facilitate loading and controlled release of therapeutic agents from nanoparticles, thereby enhancing their efficacy and limiting off-target effects. Moreover, coating materials can be functionalized with targeting ligands and imaging agents, enabling site-specific delivery of therapeutic agents and real-time monitoring of biological processes [62–64].

One commonly used coating material for cobalt oxide nanoparticles is polyethylene glycol (PEG), a biocompatible polymer known for imparting stealth properties to nanoparticles, extending their circulation time in the bloodstream, and minimizing nonspecific interactions with biological entities. The PEG coating produces a protective layer surrounding the cobalt oxide core, limiting its degradation and minimizing the risk of adverse immune responses upon administration. Furthermore, PEGylation improves the dispersibility of cobalt oxide nanoparticles in physiological fluids, leading to homogeneous distribution and enhanced targeting of cancer cells [65,66].

Another coating material is silica, a flexible inorganic coating known for its biocompatibility and ease of functionalization. Through silica coating, these therapeutic agents are anchored to cobalt oxide nanoparticles, with controlled release kinetics, by providing a stable matrix for drug retention. Moreover, silica coatings can be functionalized with targeting ligands and imaging agents that facilitate selective uptake of the particles in tumor tissue and real-time monitoring of therapeutic outcomes [67,68]. Other polymers can also be coated onto cobalt oxide nanoparticles, including albumin, chitosan, polyethylene glycol, and dendrimers, which offer additional benefits such as biocompatibility, targeting, and drug-loading capacity. Therefore, the choice of coating material is essential to enhance the function of cobalt oxide nanoparticles for drug delivery in cancer treatment, and further studies in this research field are promising for developing efficient and personalized medication approaches [69–71].

3. Synthesis Method of Cobalt Oxide Nanoparticles

The methods used for the preparation of cobalt oxide nanoparticles are classified into four types: physical, chemical, physicochemical, and biological. Further categorization is depicted in Figure 2. These techniques often use templates or stabilizing chemicals to control the size, shape, and dispersion of nanoparticles.



Figure 2. Schematic representations of various synthesis methods for cobalt oxide nanoparticles. Created in BioRender. UIPSR, P. (2025) <https://BioRender.com/pcx2a6f>.

3.1. Physical method.

Physical methods for synthesizing cobalt oxide nanoparticles provide alternatives for achieving exact control over particle properties. Different methods for the formulation of cobalt oxide nanoparticles are depicted in Figure 3.

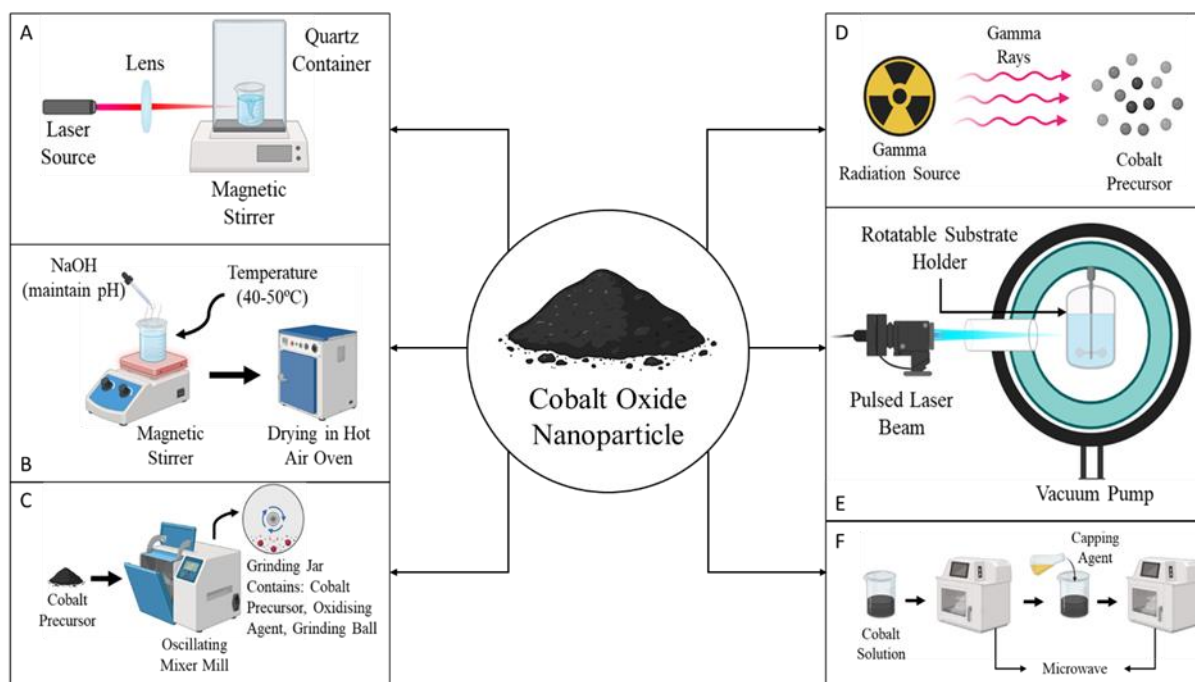


Figure 3. Visualizing Diverse Physical Synthesis Techniques: (a) Laser ablation; (b) Low-temperature synthesis; (c) Mechanochemical; (d) Radiation Technique; (e) Pulse Laser Deposition; (f) Microwave Assisted. Created in BioRender. UIPSR, P. (2025) <https://BioRender.com/crj5ioy>.

Laser ablation involves focusing a high-energy laser beam on a cobalt target in a liquid medium that contains a suitable stabilizing agent. The high laser energy causes the cobalt target to evaporate. Condensation of vaporized cobalt in liquid results in the formulation of cobalt oxide nanoparticles. This approach enables the manufacture of nanoparticles with narrow size distributions and great purity [72].

Low-temperature synthesis methods involve the formation of cobalt oxide nanoparticles at temperatures below 100°C. This method frequently uses precursor chemicals, such as cobalt nitrate, cobalt chloride, cobalt acetate, cobalt carbonate, and cobalt oxalate, which break down or react to form cobalt oxide nanoparticles under mild conditions. Sol-gel methods and hydrothermal synthesis are two examples that involve the incorporation of cobalt precursors with suitable reacting agents and heating them under controlled temperature and pressure conditions to promote nanoparticle formation [73].

Mechanochemical synthesis involves the reduction of cobalt-containing precursors, commonly via mechanical blending or mechanical milling, in the presence of oxygen or other oxidizing agents. The mechanical energy generated during milling contributes to the reaction processes that form cobalt oxide nanoparticles from the precursors. The following are some of the benefits of this technique: the technique is easy to use, the fast rate when moving from a laboratory scale to an industrial one, and it is also flexible to synthesize particles of a certain type or particles with a particular attribute, depending on the parameter of the milling operation [74].

In the radiation-based synthesis method, a specific type of radiation, such as gamma rays or electron beams, can trigger chemical reactions to synthesize cobalt oxide nanoparticles. Cobalt-containing precursors are used in the formulation of nanoparticles, and the process involves nucleation and growth. Certain radiation-based techniques involve particle size and shape, which can be effectively controlled and can operate in both aqueous and non-aqueous conditions [75].

Microwave-assisted synthesis involves cobalt-containing precursors under microwave irradiation in the presence of an appropriate solvent or surfactant. Fast microwave heating increases precursor decomposition or reactivity, enabling the preparation of cobalt oxide nanoparticles. Microwave synthesis offers benefits such as fast reaction rates, improved product uniformity, and energy savings [76].

Pulse laser deposition is a process in which a cobalt target is irradiated with intense pulsed laser beams in a controlled vacuum or inert gas environment. The deposited cobalt atoms or clusters end up on a substrate, where they begin to sinter and grow into cobalt oxide nanoparticles. The advantage of this technique is that particle size, composition, and distribution can be easily controlled on specific substrates, making it useful for thin-film deposition as well as device production [77]. In summary, each physical synthesis approach described above has its strengths and weaknesses and can be tuned to synthesize cobalt oxide nanoparticles with desired characteristics suitable for applications in catalysis, electronics, and biomedical technology.

3.2. Chemical method.

Chemical methods are important for the fabrication of cobalt oxide nanoparticles. This controllable method produces a cobalt oxide of appropriate size and shape. It produces nano-sized particles that are suitable for catalyst, electronic, and biomedical applications, with controllable, high-production capacities. Various techniques are used to synthesize cobalt oxide nanoparticles, as shown in Figure 4.

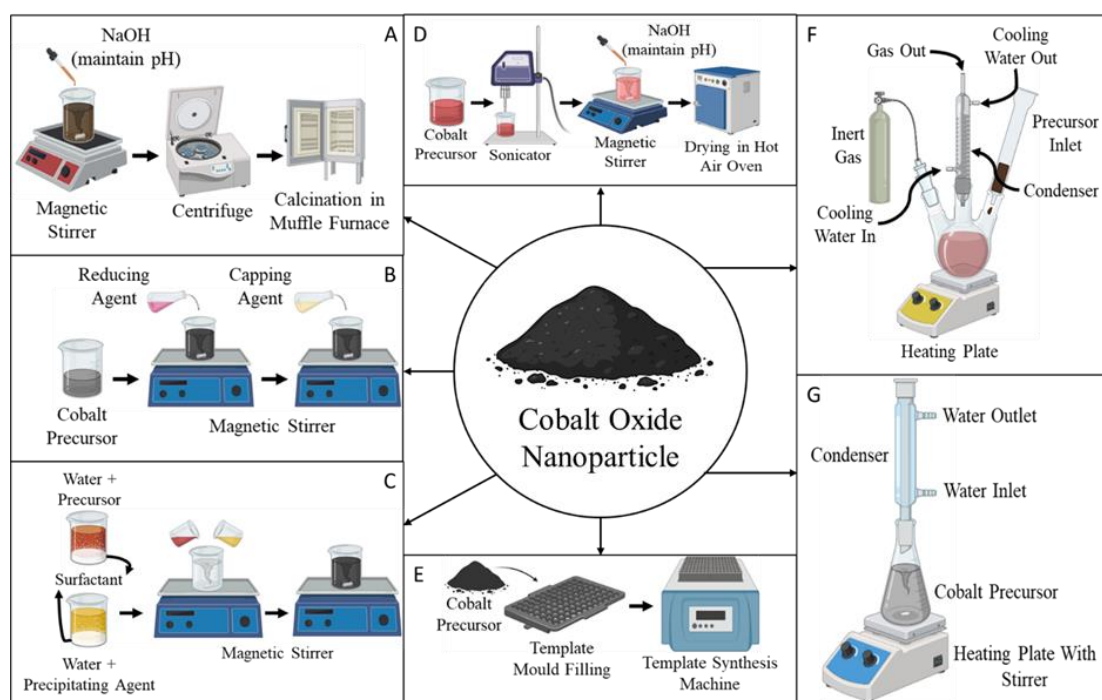


Figure 4. Visualizing Various Chemical Synthesis Techniques: (a) Chemical Precipitation; (b) Chemical Reduction; (c) Microemulsion; (d) Wet Chemical; (e) Template Synthesis; (f) Thermal Decomposition; (g) Reflux Approach. Created in BioRender. UIPSR, P. (2025) <https://BioRender.com/26nmhkj>.

Chemical precipitation is a type of cobalt deposition that refers to the formation of cobalt hydroxide nanoparticles through the controlled formation of cobalt-containing salts and a precipitating agent at a given condition. These are further thermally treated or oxidized to obtain cobalt oxide nanoparticles. It helps to follow the reaction's sequence with a high degree of control over particle size and shape by making small variations in reaction conditions, such as pH, temperature, and concentration [78].

Another technique is the chemical reduction method, which involves forming solutions containing cobalt salts and using reducing agents to reduce metallic cobalt. This may be carried out using hydrazine and sodium borohydride. The reduction reaction generates cobalt nanoparticles, which then oxidize in air or after post-treatment to yield cobalt oxide nanoparticles [79].

Thermal breakdown involves heating cobalt-containing precursors, such as metal-organic complexes or cobalt salts, to high temperatures in an inert atmosphere, thereby decomposing the precursors and producing cobalt oxide nanoparticles. Variations in temperature, heating rate, and precursor composition can be used to adjust the particle size and crystallinity of the resultant nanoparticles [80].

The template synthesis method uses pre-made templates or molds to control the size, shape, and morphology of cobalt oxide nanoparticles. Cobalt-containing precursors are then deposited within the template and subjected to chemical conversion or reduction to obtain particles with the required size and structure. This method enables the development of nanowires, nanotubes, and ordered arrays of nanoparticles [81].

Microemulsion approaches involve a surface-active agent that serves as a reaction medium for nanoparticle production. In the microemulsion, the cobalt precursors are uniformly dispersed, and a chemical reaction occurs, forming cobalt oxide nanoparticles. The surfactant used ensures that nanoparticles grow only in a specific region, thereby yielding the desired size and shape. Given several advantages, such as better stability, narrower size distribution, and the possibility of scaling up, this method is widespread [82].

A solution-based process, also known as the wet chemical process, typically involves the synthesis of cobalt oxide nanoparticles via various chemical reactions in a solvent environment. Such procedures comprise a prearranged process of adding cobalt salts with other reagents or solvents to establish certain reaction conditions. Some other factors that can be controlled include the pH of the medium, temperature, reaction time, and other factors that depend on the specific use of the resulting nanoparticles. Wet chemical synthesis is the most suitable method for the preparation of nanoparticles, as it is scalable [83].

Reflux synthesis is the process in which a substance is heated under reflux conditions (at the boiling point of the solvent used), and the solvent and the condensed product are returned to the original vessel. Cobalt-containing precursors are refluxed in suitable reagents to produce cobalt oxide nanoparticles by heating. Reflux conditions can provide the proper agitation ratio and suitable reaction rates for the synthesis of nanoparticles with the desired size, composition, and crystallinity [84].

3.3. Physicochemical method.

Physicochemical approaches combine chemical and physical procedures to formulate cobalt oxide nanoparticles with specific characteristics. These approaches employ a range of strategies to control reaction conditions and precursor interactions, enabling accurate nanoparticle fabrication. Different approaches in this category are depicted in Figure 5.

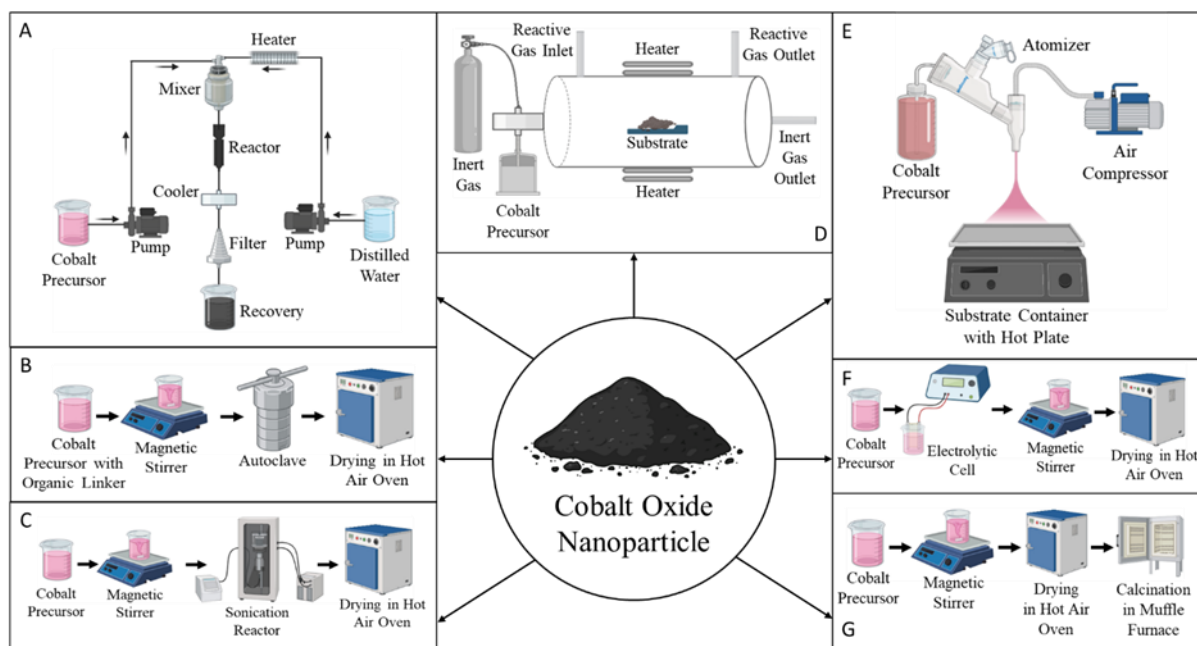


Figure 5. Visualizing Diverse Physicochemical Synthesis Techniques: (a) Supercritical Hydrothermal Synthesis; (b) Solvothermal & Hydrothermal Synthesis; (c) Sonochemical; (d) Vapour Deposition Approach; (e) Spray Pyrolysis; (f) Electrochemical; (g) Sol-Gel Synthesis. Created in BioRender. UIPSR, P. (2025) <https://BioRender.com/hemxns9>.

The supercritical hydrothermal synthesis approach involves the reaction of cobalt-containing precursors under supercritical water conditions, in which water exists as both a liquid and a gas. High-pressure and high-temperature conditions favor rapid precursor breakdown and nanoparticle nucleation, enabling the manufacture of cobalt oxide nanoparticles with controlled size and crystallinity [85].

Sol-gel process: This method involves preparing a gel matrix by dissolving a cobalt precursor in a suitable solvent. These precedents undergo hydrolysis in which water molecules are cleaved to form metallic hydroxides or oxides. Subsequent condensation reactions among these individual hydrolyzed molecules form a stable three-dimensional amorphous gel network. This is followed by other gel processing steps, such as drying and subsequent calcination, to drive out solvent molecules within the gel matrix and to induce the formation of cobalt oxide nanoparticles [86].

Solvothermal and hydrothermal processes were used to produce cobalt oxide nanoparticles at high temperatures and pressures from precursor solutions. In solvothermal synthesis, organic solvents are used, whereas hydrothermal synthesis employs water. The heating and cooling cycles of the reaction vessel can be controlled to slow or speed up the process, enabling nucleation and the successive growth of cobalt oxide nanoparticles [87].

Sonochemical synthesis is a method that applies ultrasonic waves to facilitate the formation of a cavity in a solvent solution containing cobalt compounds. As noted before, the formation and destruction of microbubbles result in elevated temperature and pressure within a specific region, thereby improving chemical reactions and generating cobalt oxide nanoparticles with uniform particle size and shape [88].

Electrochemical techniques include allowing cobalt ions to adhere to electrically conducting substrates and subsequently oxidizing them to produce cobalt oxide nanoparticles. Depending on the desired size, shape, and location of the nanoparticles on the substrate surface, they can be manipulated by the voltage applied to the electrode, the solution's ion concentration, and deposition parameters [89].

Spray pyrolysis involves using a cobalt salt-bearing precursor, which is nebulized into fine droplets and deposited into a high-temperature reactor for the preparation of nano-coatings. Removal of solvents and further breakdown of precursors results in the formation of cobalt oxide nanoparticles that deposit on a substrate or filter. This concept is especially useful for the mass production of nanoparticles [90].

Vapor deposition involves generating cobalt-containing vapor, depositing it onto a substrate, and nucleating and growing cobalt oxide nanoparticles. Chemical vapor deposition (CVD) and physical vapor deposition (PVD) methods provide greater control over the deposition process and interactions between the substrate and the deposit, yielding high-quality cobalt oxide thin films or nanostructures [91]. These physicochemical synthesis methods offer multiple strategies for the controlled creation of cobalt oxide nanoparticles, which can be fine-tuned to meet the specified properties for various applications.

3.4. Biological method.

Biological methods harness the natural processes of living organisms to synthesize cobalt oxide nanoparticles, offering eco-friendly and sustainable alternatives to traditional chemical and physical methods. Among these approaches, the most common methods are plant-mediated and fungi-mediated synthesis techniques. Both of these approaches are depicted in Figure 6.



Figure 6. Visualizing Diverse Biological Synthesis Techniques: (a) Plant Mediated; (b) Fungi Mediated. Created in BioRender. UIPSR, P. (2025) <https://BioRender.com/s4j5tgh>.

Plant-mediated synthesis is a green synthesis method in which nanoparticle formulations use plant extracts or biomass as reducing and stabilizing agents. Plant extracts mainly encompass flavonoids, phenols, and terpenoids, which reduce the cobalt ions and create cobalt oxide nanoparticles. The phytochemicals in the extracts provide an added advantage in the reduction process and also act as capping agents to stabilize the nanoparticles. This approach is useful because it is an economical, green alternative to synthetic methods that use metal catalysts, and it is easily scalable. In addition, plant-mediated synthesis enables the formulation of nanoparticles with desired shapes, sizes, and surface characteristics by selecting appropriate plant species and reaction conditions [92–94].

Another method is fungi-mediated synthesis, which uses fungal biomass or extracts to assist in reducing and settling cobalt ions during nanoparticle formation. Fungi contain a set of enzymes, proteins, and secondary metabolites that help reduce and trap reagents in nanoparticle synthesis. The following are the advantages of this technique: it is less harsh, as it uses mild reactions; it is scalable, as it uses fungal fermentation techniques; and different fungi possess different metabolic abilities, which can produce nanoparticles with different properties. Plant-mediated and fungi-mediated synthesis methodologies for the eco-friendly synthesis of cobalt oxide nanoparticles have been demonstrated to be useful for catalytic applications, wastewater treatment, and biomedical applications [95,96].

Table 1. Various studies reported the formulation of cobalt oxide nanoparticles.

Sl No	Synthesis method	Procedure	Capping agent used	Size (nm)	Advantages	Limitations	Ref.
1	Pulsed laser ablation method	High-quality cobalt was immersed in distilled water before being exposed to a 1064 nm pulsed Nd: YAG laser. The laser beam had a diameter of 6mm and was narrowed to around 30 μm on the target surface. Then, the properties of the resultant nanoparticles were investigated to better understand how laser fluence affects them.	Not used	18.5-46.40	Simple and prevents surface contamination	Difficult in the scale-up process for industrial production	[97]
2	Mechano-chemical synthesis method	Cobalt oxide nanoparticles were synthesized by mixing cobalt nitrate and ammonium hydrogen carbonate in a mortar/pestle, followed by milling for 2 hours and heating at 300°C for 2 hours. The resulting material is then rinsed with deionized water and dried in an oven for 12 hours.	Not used	18.4	It is a low-cost process that produces small-particle-sized nanoparticles	Development of agglomerates, presence of impurities	[98]
3	Low-temperature synthesis method	This approach includes dissolving carbon black in ethanol, adding manganese and cobalt salts, and integrating potassium hydroxide into it. The mixture is then heated to 60°C for 24 hours, then separated, rinsed, and dried. Then the product is ground to a powder.	Not used	5	Reduces energy consumption and produces ultrasmall and homogeneous nanoparticles.	It may not be suitable for producing other types of metal oxides, which involve the usage of toxic substances like KOH and metal acetates.	[99]
4	Precipitation method	Pluronic F-127 is mixed in deionized water, followed by the addition of cobalt nitrate, and Co ₃ O ₄ nanoparticles are precipitated. The mixture is agitated, recovered, and filtered. The precipitates are dried, calcined, and filtered to create black Co ₃ O ₄ nanoparticles.	Pluronic F-127	10-20	Simple, cost-effective, scalable, produces highly pure nanoparticles	Requires long reaction time, high energy consumption, and high calcination temperature, which may affect the properties of nanoparticles.	[100]
5	Chemical reduction method	The technique begins by injecting salt and alkali solutions into a reactor, where they undergo a reaction. The mixture is then stirred to achieve an even distribution. The resultant colloid is then purified by washing with distilled water and ethanol. Once cleansed, the colloid is transported to a quartz reactor at a temperature of 220°C for metallization	Not used	43	Provides high saturation magnetization and controls synthesis parameters	Time-consuming and requires high energy	[101]
6	Thermal decomposition method	Cobalt nanoparticles are formulated by combining cobalt chloride hexahydrate and carboxymethyl cellulose solutions, and then a gradual addition of hydrazine hydrate and ascorbic acid. This reaction turned the solution from pink to clear	Carboxy Methyl Cellulose (CMC)	<100	Fast and simple, produced high surface area and porous nanoparticles	Showed lower catalytic activity, the nanoparticles are not crystalline.	[102]

Sl No	Synthesis method	Procedure	Capping agent used	Size (nm)	Advantages	Limitations	Ref.
		brown, and then the application of microwave irradiation to the mixture transformed the solution into translucent brown cobalt nanoparticles.					
7	Soft template method	This method uses a microemulsion solution of CTAB, water, and hexanol. Metal salts and a reducing agent are held in separate microemulsions. Mixing these solutions in the presence of argon allows for regulated nucleation and growth of nanoparticles. Impurities and surfactants are removed via centrifugation and washing. Finally, annealing at 550°C for 30 minutes improves crystallinity and magnetic properties, making the nanoparticles suitable for various applications.	Cetyltrimethylammonium bromide (CTAB)	50	The approach can formulate controlled-size nanoparticles and can obtain a substantial magnetization of nanoparticles.	It may cause slight surface oxidation and may involve the phase transition of a soft template system affecting the shape of the nanoparticles.	[103]
8	Micro-emulsion method	Accurately weighed FeCl ₃ ·6H ₂ O and CoCl ₂ ·6H ₂ O solutions were mixed in distilled water. Then, 2.3 M NaOH solution was prepared by dissolving crushed sodium hydroxide pellets in distilled water to maintain pH values. Oleic acid served as a capping agent to prevent agglomeration. The procedure involved stirring the solution at 85°C for 2 hours, then cooling to room temperature, filtering, and washing. Centrifugation was then conducted, followed by drying in an oven. Finally, annealing at 900°C was performed to enhance crystallinity and properties.	Oleic acid	13.79–30.40	Increases the precision and control over the size and structure of the nanoparticles, making it possible to produce very pure and narrowly distributed nanoparticles.	It requires careful adjustment of pH and may cause agglomeration.	[104]
9	Wet-chemical method	The principle involves controlled thermal decomposition of octadecyl amine and cetyltrimethylammonium bromide (CTAB) in an argon-inert environment. The mixture is then degassed to remove contaminants. Cobalt carbonyl is introduced as a precursor catalyst and heated to 200°C to form nanoparticles, which are then washed and cleaned with ethanol and hexane.	Octa-decyl amine	50-100	The nanoparticles exhibit long-lasting durability	High energy consumption and uncontrolled size distribution.	[105]
10	Supercritical hydrothermal method	In this method, metal-containing precursors are deliberately precipitated to form solid products at a certain pH. After dissolving gallium nitrate and cobalt nitrate hexahydrate in water, the pH was adjusted by the addition of sodium hydroxide solution. The solution was heated to 400°C and then rapidly cooled to terminate the reaction. The synthesized solid product was centrifuged, decanted, and freeze-dried for further characterization.	Not used	10-53	Inexpensive and environmentally friendly	Difficult in dissolving the nanoparticles for further analysis & can cause contamination.	[106]
11	Sol-gel method	Cobalt nitrate hexahydrate is dissolved in ethylene glycol with a ratio of 1:3, followed by stirring and drying at 120°C, pulverized to get a powdered sample, and sintered at 700°C.	Not used	90-250	Simple and low-cost	It may create a high oxygen level.	[107]
12	Solvothermal method	In this process, a carefully regulated chemical reaction is used to create cobalt oxide nanoparticles. Cobalt (II) and (III) acetylacetonate are dissolved in ethanol and water, followed by hydrogen peroxide and sodium hydroxide. The mixture is stirred to ensure uniformity, then heated at different temperatures for 8 hours, dried, and calcined at 500°C for 5 hours to obtain cobalt oxide nanoparticles.	Not used	40	Simple, versatile, and low-cost method	It requires a long reaction time and high reaction temperature. The use of cobalt acetylacetonate may introduce impurities.	[108]

Sl No	Synthesis method	Procedure	Capping agent used	Size (nm)	Advantages	Limitations	Ref.
13	Sonochemical method	The process of producing cobalt oxide nanoparticles is based on the thermal conversion of a precursor chemical $[\text{Co}(\text{PDC})_2(\text{H}_2\text{O})_2]_n$ in a static air environment at different temperatures. First, the precursor material is thermally treated for five hours at 400°C, 600°C, 800°C, and 850°C, in the presence of oxygen. Consequently, the precursor undergoes chemical processes that culminate in the formulation of cobalt oxide nanoparticles.	Not used	30-80	Can produce nanoparticles of different sizes and morphologies, low cost and versatile	Requires high irradiation time, may cause decomposition	[109]
14	Electrochemical	Using electrochemical reduction in an electrolyte made from CoCl_2 and SmCl_3 dissolved in the ionic liquid BMPTFSA, Co-Sm nanoparticles are synthesized. A glassy carbon working electrode, a platinum wire counter electrode, and a silver wire reference electrode are used in a three-electrode cell to facilitate the reduction process at 25°C. The potential is scanned at a rate of 50 mV/s, cycling between -1.2 V and 1.2 V. SmCo_7 nanoparticles are created during reduction when electrochemically produced Sm(II) ions combine with Co(II) ions. BMPTFSA acts as a protective layer, stabilizing these nanoparticles in air. Furthermore, the development of SmCo_7 nanowire-shaped deposits during potentiostatic cathodic reduction is facilitated by placing a magnet behind the glassy carbon electrode.	1-Butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonylethyl)sulfonylimide (BPMPTFSA)	<20	It can provide the controlled synthesis of nanoparticles, and it can be easily scaled up.	Need a thorough understanding of the reaction mechanism of the synthesis of nanoparticles.	[110]
15	Plant-mediated synthesis method	The methanolic extract of <i>C. roseus</i> is used in the green synthesis of cobalt nanoparticles (CoNPs). Plant material is first collected, dried, and then processed into a fine powder. The phytochemicals are then extracted by heating this powder using methanol. Following that, the methanolic extract is gradually added, while stirring constantly and at a high temperature, to an aqueous solution of cobalt chloride (CoCl_2). The extract's phytochemicals function as reducing agents to speed up the transformation of Co^{2+} ions into CoNPs. The reaction mixture's hue shift signifies the production of CoNPs. The produced nanoparticles are collected, centrifuged, washed, and dried for additional examination.	Cetyltrimethylammonium bromide (CTAB)	27.08	Simple and easy, environmentally friendly, cost-effective, and biocompatible	Poor reproducibility and low yield require post-synthesis purification	[111]
16	Fungal-mediated synthesis method	The microbe, <i>P. prolifica</i> , is cultivated in a YMG 50% seawater medium and cultured for five days in rotating flasks. The supernatant is then treated with cobalt chloride (CoCl_2) to measure extracellular bio-reduction. A metal salt solution is produced, and some of the supernatant is added to it, causing bio-reduction leading to the formation of cobalt nanoparticles.	Not used	21	Simple, cost-effective, and eco-friendly, the developed nanoparticles also have antibacterial properties.	Time-consuming and requires in-depth, thorough studies on marine fungi.	[112]
17	Radiation technique	Cobalt ions are converted to cobalt atoms when gamma radiation is applied to a solution of cobalt dichloride in isopropanol that has been stabilized with the capping agent polyvinylpyrrolidone. Cobalt nanoparticles are created when these freshly generated atoms combine because of their strong reactivity.	Polyvinylpyrrolidone (PVP)	7-12	Produces fully reduced size and highly pure nanoparticles	Requires a high-energy radiation source and may cause unwanted oxidation of metal ions.	[113]

Sl No	Synthesis method	Procedure	Capping agent used	Size (nm)	Advantages	Limitations	Ref.
18	Microwave-assisted synthesis method	Cobalt and iron salts were carefully combined with mineralizing agents, NH ₄ OH and KOH, in a precise ratio and concentration to create cobalt ferrite (CoFe ₂ O ₄). In a microwave reactor, this combination underwent hydrothermal treatment, which involved a slow increase in temperature of 10°C per minute to 140°C. To create the required powder, the resultant samples were cooled, cleaned, and dried.	Chitosan	5.2-19.1	It can produce nanoparticles of controlled size; it also enhances the magnetic properties of the nanoparticle	Lack of reproducibility	[114]
19	Reflux method	The synthesis presented is based on the concept of cobalt hydroxide gel formation via a precipitation process. First, a solution is created by dissolving cobalt chloride hexahydrate (CoCl ₂ ·4H ₂ O) in 10 ml double-distilled water. Cobalt hydroxide gel precipitate takes on a blue hue when NH ₄ OH solution is added, triggering a chemical reaction. After that, the gel is heated for four hours at 100°C while in reflux, which helps the gel change into a more stable form and gets rid of any leftover solvent. The final product is then cleaned with ethanol and water to get rid of any leftover chemicals and contaminants. Ultimately, the final cobalt hydroxide nanoparticle is obtained by drying the cleaned product for ten hours at 70°C.	Not used	19	A simple, traditional method can achieve large-scale synthesis	Can contain impurities, and may not be able to produce nanoparticles of uniform shape and size	[115]
20	Arc discharge method	Ultrasonic nebulization creates a cobalt precursor solution, which is transformed into nanoparticles through an arc discharge procedure. This process involves high-frequency sound waves, argon gas, and graphite rods. The high temperature and energy produced by the arc discharge vaporize and decompose the cobalt atoms, preventing oxidation to create cobalt nanoparticles.	Not used	15.53	Produces highly pure nanoparticles and develops controlled size distribution and dispersion	Requirements of specific equipment and challenges in scaling up the process	[116]
21	Spray pyrolysis method	A cobalt nitrate solution is atomized and sprayed into a hot reactor during the spray pyrolysis stage. Cobalt oxide (Co ₃ O ₄) microspheres are created when cobalt nitrate breaks down due to the high temperature within the reactor. Subsequently, the Co ₃ O ₄ microspheres undergo a hydrogen atmosphere at different temperatures during the hydrogen reduction process. The cobalt oxide is chemically converted to metallic cobalt in this reducing atmosphere.	Not used	27-88	Simple and versatile, it can produce spherical aggregates of nanoparticles	Requires high temperature, which can cause agglomeration	[117]
22	Vapor deposition method	A Co(NO ₃) ₂ /NaCl combination is produced by drying the solution after it has been thoroughly mixed. The Co/NaCl catalyst precursor is created by calcining this combination at 350°C in argon gas. To create the Co/NaCl catalyst, the Co/NaCl precursor is then reduced in hydrogen gas at the same temperature. By heating the Co/NaCl catalyst in a combination of argon and acetylene gases to 400°C, cobalt nanoparticles may be carbon encapsulated. The material is ultrasonically sonicated in distilled water to separate the precipitate and purify the resultant carbon-encapsulated cobalt nanoparticles. The final product is obtained by drying the solid precipitates.	Not used	15-30	Produced nanoparticles with a uniform size distribution, exhibiting good electromagnetic and microwave-absorbing properties	The use of acetylene may induce safety-related problems; the procedure cannot be applied in large-scale production.	[118]

4. Applications

4.1. Theranostic applications.

Cobalt nanoparticles have emerged as powerful theranostic tools, effortlessly merging therapeutic and diagnostic functions into a single platform. They have a wide range of therapeutic applications due to their unique characteristics [119]. Some of the theranostic tools are discussed below:

4.1.1. Magnetic resonance imaging (MRI) technique contrast agents.

Because of their excellent relaxivity values, cobalt nanoparticles may have promising potential as positive and negative contrast agents in MRI [120]. Their smaller size, along with cobalt's higher saturation magnetization, enables the use of smaller nanoparticles while preserving sensitivity, resulting in improved MR contrast and consistent imaging across various body regions [121]. Arshad *et al.* have shown that cobalt ferrite nanoparticles, with their high coercivity, low saturated magnetization, and biocompatibility, exhibit strong efficacy as MRI contrast agents for improving visual contrast in liver and spleen tissues. Notably, they yield higher signal intensity in T2-weighted MRI images than normal iron oxide nanoparticles, suggesting they could be used as alternative MRI contrast agents to diagnose a range of illnesses. Likewise, these nanoparticles sustain the viability and potential of brain stem cells, allowing for non-invasive surveillance following transplantation [122]. Hence, owing to these excellent qualities, magnetic cobalt ferrite spinel nanoparticles also offer dual functionality for targeted drug delivery and MRI monitoring, making them useful for developing therapeutics for cancer, spinal cord injuries, and other central nervous system conditions, as reported by Mikhaylov *et al.* [123].

4.1.2. Photothermal therapy (PTT).

Cobalt nanoparticles exhibit strong near-infrared (NIR) absorption, making them suitable for photothermal therapy. They generate heat when exposed to NIR irradiation, resulting in regional hyperthermia and selective death of target cells, including cancer cells. When combined with imaging techniques, PTT enables accurate therapy-guiding and monitoring of therapeutic response [124]. Meanwhile, cobalt phosphide nanoparticles demonstrate effective triple-modal imaging, including infrared thermal (IRT), photoacoustic (PA), and T2-weighted magnetic resonance (MR) imaging, enabling complete cancer identification. They also exhibit excellent near-infrared absorption and high photothermal conversion efficiency, making them intriguing candidates for photothermal treatment (PTT) to selectively kill cancer cells. Importantly, the biocompatibility and stability of the nanoparticles in different physiological conditions indicate their potential for biomedical applications [125]. In a related study, Zhang *et al.* developed PEG-modified cobalt carbide nanoparticles (Co₂C-PEG NPs) as cancer photothermal theranostic agents. These nanoparticles exhibited high photothermal conversion efficiency and good stability, enabling effective tumor monitoring and PTT efficacy both *in vitro* and *in vivo* [126]. In another study, Motorzhina *et al.* investigated composite nanoparticles with a gold core enveloped by cobalt ferrite, highlighting the importance of optimizing the gold-to-cobalt ferrite ratio to improve treatment efficiency. Their research demonstrated that a 100 µg/ml solution increased the temperature by ~8.2 K and achieved a photothermal conversion efficiency of ~51%, resulting in a 22% reduction in cell

viability [127]. Furthermore, Najafabad *et al.* showed that combining PTT with photodynamic therapy (PDT) significantly enhances therapeutic effects against cancer cells, overcoming resistance mechanisms. This combination of therapies holds great potential for advancing cancer treatment [128].

4.1.3. Stimuli-responsive drug delivery.

Stimuli-responsive cobalt nanoparticles are designed to release medication in response to specific stimuli, such as changes in pH, temperature, or enzyme activity. This allows for exact control over the administration of medications. [129]. These nanoparticles have potential for targeted therapy because they can be designed to respond to the microenvironment of diseased tissues, reducing systemic adverse effects. As reported by Ruttiger *et al.*, block polymers are known to be redox-sensitive, and polymers containing cobalt can be transformed into magnetic ceramics. As a result, these characteristics make them excellent for usage in a variety of applications, such as selective release mechanisms, nanolithography, and magnetic device fabrication [130]. Also, Dey *et al.* found that cobalt ferrite nanoparticles appear to be versatile tools capable of addressing critical issues in targeted cancer treatment by combining responsiveness, biocompatibility, and therapeutic effectiveness for future medical applications. They exhibit a drug-delivery mechanism that is sensitive to tumor-like conditions of temperature and pH. The observed increase in drug release at high temperatures and acidic pH indicates that they are suitable for localized therapy with minimal systemic effects. Furthermore, their demonstrated biocompatibility ensures safe use in cancer therapy, which is reinforced by their non-toxicity [131].

4.1.4. Targeted therapy.

Cobalt nanoparticles are used for targeted treatment and possess cytotoxic effects on defective cells through activities such as reactive oxygen species (ROS) formation. Alarifi *et al.* and Lugun *et al.* found that by guiding these nanoparticles toward these cells and inducing ROS generation, oxidative stress is increased, leading to selective killing of the target cells with minimal impact on healthy cells [132,133]. It offers the potential to develop better and safer drugs for many diseases due to its accuracy. Also, Chattopadhyay *et al.* reported that targeting could be achieved by surface modification of cobalt oxide nanoparticles, for instance, using N-Phosnomethyliminodiacetic acid (PMIDA), which can decrease the toxicity of the nanoparticles. PMIDA alteration of these nanoparticles makes them tumor-associated antigens that also interact with human macrophages, as shown in a study. The results show that PMIDA-coated cobalt oxide nanoparticles can activate T cells to attack oral carcinoma cells and thus serve as a platform for cancer immunotherapy [134].

4.1.5. Biosensors.

Cobalt nanoparticles are widely used in biosensors due to their larger surface area and superior catalytic performance, enabling the identification of target analytes. These biomolecule-functionalized nanoparticles offer enhanced selectivity and are seen as a potential improvement over current biomedical diagnostics [135]. Ali *et al.* demonstrated that, in the field of biosensors, cobalt oxide nanoparticles are promising, as evidenced by the development of a potentiometric biosensor using chitosan/cobalt oxide (CS/Co₃O₄) nanocomposites and the enzyme urease. These nanoparticles have ferromagnetic properties that enhance the biosensor's

excellent sensitivity, selectivity, and reproducibility, while maintaining stable response time. A critical aspect highlighted in the study is the biosensor's environmental friendliness and simplicity, and the enhancement of biosensors through the incorporation of cobalt oxide nanoparticles [136]. Also, Karupppiah *et al.* reported that together with the enhancement of the rate of electron transfer, sensitivity, and reaction times through cobalt oxide nanoparticles, this has made it possible to accommodate the development of efficient enzymatic glucose biosensors and nonenzymatic hydrogen peroxide sensors, which would point towards the sensitivity of glucose and hydrogen peroxide in various applications [137]. Moreover, Erden *et al.* also demonstrated the suitability of cobalt nanoparticles for enhancing xanthine content in fish samples to assess fish freshness [138]. Therefore, cobalt oxide nanoparticles play a very important role in enhancing biosensor performance by improving electronic transfer and sensitivity, which may pay off across several sectors.

5. Future Prospective

The advancement of cobalt nanoparticle research uncovers various valuable fields for further investigation in cancer therapy. This involves improving functionalization methods [139,140] and creating hybrid nanostructures that produce beneficial and synergistic effects [141, 142]. One major concern is that the production of drug-delivery systems that respond to external stimuli is highly feasible with CoNPs. Future projects may emphasize the use of external signals, such as electromagnetic fields, to steer therapeutic release to targeted areas for improved cancer therapy [143, 144]. Future studies might focus on developing more environmentally friendly synthesis methods for CoNPs to address growing concerns about sustainability. Including plant extracts, microorganisms, and bio-derived components in synthesis would help minimize environmental impacts and promote a more sustainable approach to producing CoNPs [145].

6. Conclusion

Numerous intricate investigations on the synthesis of CoNPs have been prompted by the growing interest in them. Scientists must devise a straightforward, efficient process for synthesizing cobalt nanoparticles and investigate the critical variables that influence the final nanoparticles' physicochemical characteristics. The primary areas of interest for this review include cobalt nanoparticle synthesis methods and their uses in diagnostic materials, cancer treatment, and catalysis. This paper also highlighted the major studies reported by various researchers on the formulation of cobalt nanoparticles. However, it is still necessary to make a significant shift from laboratory to industrial research. Cobalt nanoparticles can be used as drug carriers, delivering medication to affected areas while sparing healthy tissue. Furthermore, the targeting of drug delivery can be enhanced by magnetic properties. As a result, focus must be placed on formulating novel dosage forms that can reduce adverse effects and improve the efficacy of active pharmaceutical ingredients at the lowest possible concentration. The potential of cobalt nanoparticles in cancer therapy is particularly notable. Their ability to enhance drug delivery and selectively target cancer cells opens new possibilities for personalized medicine and combination therapies. The magnetic properties of CoNPs also enable their use in hyperthermia treatments and MRI-guided drug delivery, further expanding their application in cancer diagnosis and therapy. Despite these promising advancements, several challenges remain, including the need to optimize synthesis methods for large-scale

production and the limited data on the long-term biocompatibility and toxicity of cobalt nanoparticles. Future research should address these gaps by improving the scalability of production processes, enhancing the functionalization of CoNPs to improve targeting efficiency, and thoroughly evaluating their *in vivo* safety profiles. In addition, exploring the theranostic capabilities of cobalt nanoparticles combining therapeutic and diagnostic functions could significantly advance cancer treatment. By addressing these critical areas, cobalt nanoparticles have the potential to revolutionize cancer therapy, offering more effective and personalized treatment options for patients.

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Conflicts of Interest

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