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Green Synthetic Approach for the Preparation of Rifaximin Using Eco-Friendly Copper Oxide Nanoparticle Catalysis

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Abstract: *The increasing environmental concerns associated with conventional pharmaceutical synthesis have created significant interest in the development of sustainable and eco-friendly synthetic methodologies. The present study focuses on a green synthetic approach for the preparation of rifaximin using copper oxide (CuO) nanoparticles as an eco-friendly heterogeneous nanocatalyst. Rifaximin is a semisynthetic rifamycin derivative widely used in the treatment of gastrointestinal infections, traveler's diarrhea, hepatic encephalopathy, irritable bowel syndrome, and bacterial overgrowth disorders because of its broad-spectrum antibacterial activity and minimal systemic absorption.*

Conventional synthetic procedures for rifaximin often involve toxic solvents, hazardous reagents, high energy consumption, and environmentally harmful reaction conditions, which may generate significant chemical waste and environmental pollution. In the present work, CuO nanoparticles were synthesized through a green plant-mediated method using citrus leaf extract, where naturally occurring phytochemicals acted as reducing, stabilizing, and capping agents during nanoparticle formation.

The synthesized CuO nanoparticles were characterized using UV–Visible spectroscopy, Fourier Transform Infrared Spectroscopy (FTIR), X-ray Diffraction (XRD), and Scanning Electron Microscopy (SEM). UV–Visible spectroscopic analysis confirmed characteristic nanoscale absorption in the range of 250–350 nm, while XRD analysis revealed the formation of monoclinic crystalline CuO nanoparticles. FTIR spectroscopy confirmed Cu–O bond formation along with phytochemical stabilization of the nanoparticles, and SEM analysis indicated spherical and agglomerated nanosized particle morphology.

The synthesized CuO nanoparticles were successfully utilized as recyclable heterogeneous catalysts during the multistep synthesis of rifaximin intermediates and final products. The developed catalytic methodology demonstrated several advantages including shorter reaction time, improved product yield, enhanced selectivity, reduced toxic waste generation, and environmentally benign reaction conditions. The synthesized rifaximin was further characterized using UV spectroscopy, FTIR spectroscopy, NMR spectroscopy, and chromatographic analysis to confirm structural integrity and purity.

Overall, the present study demonstrates that CuO nanoparticle-assisted green synthesis provides an efficient, sustainable, and industrially applicable approach for the preparation of pharmaceutically

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important rifamycin derivatives under eco-friendly conditions.

Keywords: Rifaximin, green chemistry, copper oxide nanoparticles, nanocatalysis, sustainable pharmaceutical synthesis, eco-friendly catalysis, rifamycin derivatives.

I. INTRODUCTION

Green chemistry has emerged as an important approach in pharmaceutical synthesis because it focuses on the reduction of hazardous chemicals, prevention of toxic waste generation, improvement of atom economy, enhancement of energy efficiency, and development of sustainable synthetic methodologies. Conventional pharmaceutical manufacturing frequently involves the use of toxic organic solvents, corrosive reagents, harsh reaction conditions, and environmentally hazardous by-products, which may contribute to environmental pollution and increased health risks. Therefore, the development of environmentally benign and sustainable synthetic routes has become highly significant in modern medicinal and industrial chemistry.

Rifaximin is a semisynthetic rifamycin derivative belonging to the rifamycin class of antibiotics and possesses the molecular formula C_{43}H_{51}N_3O_{11}. It is widely recognized for its broad-spectrum antibacterial activity and is extensively used in the treatment of traveler's diarrhea, irritable bowel syndrome (IBS), hepatic encephalopathy, small intestinal bacterial overgrowth (SIBO), inflammatory bowel diseases, and various gastrointestinal infections. Due to its poor systemic absorption, rifaximin mainly acts locally within the gastrointestinal tract, thereby reducing systemic toxicity and improving patient tolerance.

The antibacterial activity of rifaximin arises from its ability to inhibit bacterial RNA synthesis through binding with bacterial RNA polymerase. The mechanism of action can be represented as:

\text{Rifaximin + RNA\ Polymerase \rightarrow Inhibition\ of\ RNA\ Synthesis}

This inhibition interferes with bacterial transcription processes, ultimately preventing bacterial growth and survival. The pharmaceutical advantages of rifaximin include broad-spectrum antibacterial activity, localized intestinal action, minimal systemic absorption, reduced systemic toxicity, and excellent patient tolerance, making it an important therapeutic agent in gastrointestinal medicine.

Despite its therapeutic importance, conventional synthetic methods for rifaximin often involve hazardous solvents, multistep reaction pathways, prolonged reaction times, high reaction temperatures, and generation of toxic chemical waste. These limitations increase production costs and create environmental concerns associated with pharmaceutical manufacturing. Consequently, there is a growing need for green synthetic methodologies that minimize environmental impact while maintaining high reaction efficiency and product quality.

Green synthesis aims to reduce environmental pollution, minimize hazardous waste generation, improve catalytic efficiency, and develop sustainable industrial processes. Therefore, incorporation of green chemistry principles and nanocatalytic approaches in rifaximin synthesis offers an environmentally friendly and industrially viable alternative to conventional pharmaceutical synthetic methods.

Copper oxide (CuO) nanoparticles have attracted considerable attention in nanotechnology and catalytic chemistry because of their unique physicochemical properties and wide range of industrial and pharmaceutical applications. CuO nanoparticles possess high surface area, excellent catalytic activity, semiconducting behavior, thermal stability, and environmentally friendly catalytic properties, making them highly suitable for sustainable organic synthesis and pharmaceutical manufacturing. Due to their nanoscale dimensions and enhanced surface reactivity, CuO nanoparticles provide improved catalytic efficiency and faster reaction kinetics compared to conventional catalysts.

The use of CuO nanoparticles as heterogeneous nanocatalysts offers several important advantages in organic synthesis. Their high surface area enhances catalytic activity by providing a greater number of active sites for chemical reactions. The heterogeneous nature of the catalyst allows easy recovery and recyclability, thereby supporting sustainable and eco-friendly synthesis. CuO nanocatalysts also promote faster reaction kinetics, resulting in reduced reaction times and improved process efficiency. In addition, enhanced selectivity provided by the nanocatalyst improves product purity and minimizes formation of undesirable side products. These advantages make CuO nanoparticles highly effective catalysts for green pharmaceutical synthesis.

The primary objectives of the present study were to develop a green synthetic approach for rifaximin preparation, synthesize CuO nanoparticles using eco-friendly methods, and utilize the synthesized CuO nanoparticles as efficient heterogeneous catalysts during pharmaceutical synthesis. Secondary objectives included reduction of hazardous waste generation, improvement of reaction efficiency, and development of sustainable pharmaceutical manufacturing processes based on green chemistry principles.

The green synthesis of CuO nanoparticles was carried out using citrus leaf extract as a natural reducing and stabilizing medium. Citrus leaf extract contains various phytochemicals such as flavonoids, polyphenols, alkaloids, and terpenoids. These biomolecules act as reducing agents during nanoparticle formation, while simultaneously functioning as capping and stabilizing agents that prevent excessive agglomeration and enhance nanoparticle stability. This plant-mediated synthetic approach provides an environmentally benign, low-cost, and sustainable method for the preparation of CuO nanoparticles suitable for nanocatalytic applications in pharmaceutical synthesis.

II. MATERIALS REQUIRED

The materials required for the present study included various analytical grade chemicals such as copper sulfate or copper nitrate, ethanol, distilled water, palladium on carbon, sodium hydride, triethylamine, and phosphorus oxychloride ($POCl_3$). Copper salts were used as precursor materials for the synthesis of copper oxide nanoparticles, while other reagents were utilized during different stages of rifaximin synthesis and catalytic transformations. Ethanol and distilled water were used as solvents for nanoparticle preparation, purification, and reaction processes.

Fresh citrus leaves were used as the biological material for the green synthesis of CuO nanoparticles. The phytochemicals present in the citrus leaf extract acted as natural reducing, stabilizing, and capping agents during nanoparticle formation, thereby eliminating the need for hazardous chemical reducing agents.

Various analytical instruments and laboratory equipment were employed during synthesis and characterization studies. UV–Visible spectrophotometry was used for optical characterization of nanoparticles, FTIR spectroscopy for identification of functional groups and Cu–O bond formation, XRD analysis for determination of crystalline structure, and SEM analysis for studying nanoparticle morphology and surface characteristics. A magnetic stirrer was used to maintain uniform mixing during reactions, and a muffle furnace was employed for drying and calcination of the synthesized nanoparticles.

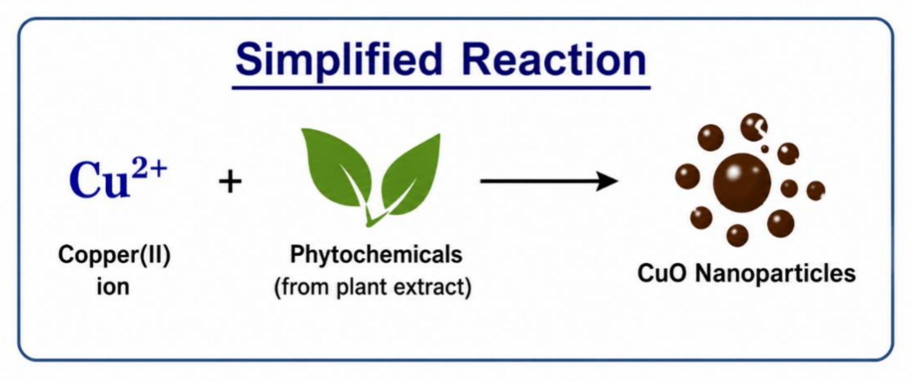
Synthesis of CuO Nanoparticles

Copper oxide nanoparticles were synthesized through an eco-friendly green synthetic method using citrus leaf extract. Initially, fresh citrus leaves were washed thoroughly with distilled water to remove dust and impurities. The leaves were then boiled in distilled water for approximately 15–20 minutes to extract bioactive phytochemicals. The resulting extract was filtered and stored for further nanoparticle synthesis.

In the next step, copper sulfate was dissolved in distilled water to prepare the copper salt precursor solution. The citrus leaf extract was then added dropwise into the copper salt solution under continuous stirring conditions. The reaction mixture was heated at 60–80°C to facilitate nanoparticle formation. During the reaction, a gradual color change from blue to green and finally to dark brown was observed, indicating the formation of CuO nanoparticles.

The precipitated nanoparticles were separated by filtration and repeatedly washed to remove impurities and unreacted materials. The obtained product was dried at 80–100°C followed by calcination at 400–500°C to obtain crystalline copper oxide nanoparticles. The successful formation of crystalline CuO nanoparticles was subsequently confirmed through spectroscopic and microscopic characterization studies.

REACTION MECHANISM



III. CHARACTERIZATION OF CuO NANOPARTICLES

UV–Visible Spectroscopy

UV–Visible spectroscopic analysis of the synthesized CuO nanoparticles exhibited a broad absorption band in the range of 250–350 nm. The observed absorption confirmed the successful formation of copper oxide nanoparticles and indicated charge transfer transitions occurring within the CuO nanostructure. The optical properties of the nanoparticles were further evaluated by estimating the band gap energy using the relation:

where (E_g) represents the band gap energy, (h) is Planck's constant, (c) is the speed of light, and (\lambda) is the wavelength of absorption. The calculated band gap value confirmed the semiconducting nature of the synthesized CuO nanoparticles.

X-Ray Diffraction (XRD) Analysis

X-ray diffraction analysis was carried out to investigate the crystalline structure and phase purity of the synthesized nanoparticles. The diffraction analysis follows Bragg's law:

n\lambda = 2d\sin\theta

Characteristic diffraction peaks observed at 2θ values of 32.5°, 35.5°, 38.7°, 48.7°, and 53.5° corresponded to the crystal planes (-110), (111), (111), (-202), and (020), respectively. These diffraction peaks confirmed the monoclinic crystalline structure of CuO nanoparticles and indicated the formation of crystalline nanosized particles. The average crystallite size was calculated using the Debye–Scherrer equation:

where (D) represents crystallite size, (K) is the Scherrer constant, (\lambda) is the wavelength of X-rays, (\beta) is the full width at half maximum (FWHM), and (\theta) is the diffraction angle.

FTIR Analysis

FTIR spectroscopic analysis was performed to identify the functional groups associated with the synthesized nanoparticles and to confirm Cu–O bond formation. Broad absorption bands observed between 3200–3500 cm^{-1} corresponded to O–H stretching vibrations, while peaks appearing between 1600–1650 cm^{-1} were attributed to C=O and C=C stretching vibrations of phytochemicals present in the citrus leaf extract. A characteristic absorption band observed in the range of 500–600 cm^{-1} corresponded to Cu–O stretching vibrations, confirming successful formation of copper oxide nanoparticles. The presence of organic functional groups further indicated phytochemical stabilization and capping of the nanoparticles.

Scanning Electron Microscopy (SEM)

SEM analysis revealed that the synthesized CuO nanoparticles possessed spherical morphology with agglomerated structures and rough surface texture. The nanoparticles exhibited nanoscale dimensions along with slight aggregation due to high surface energy and intermolecular interactions. The rough and porous surface morphology contributes to enhanced surface area, which is advantageous for catalytic applications and improved reaction efficiency in heterogeneous nanocatalysis.

Step 1: Preparation of Precursor A

The synthesis of rifaximin was initiated through catalytic hydrogenation of an aromatic precursor under mild reaction conditions. The reaction was carried out in ethanol solvent using hydrogen gas (H_2) in the presence of palladium on carbon (Pd/C) catalyst. The catalytic hydrogenation process facilitated selective reduction of the precursor compound, leading to the formation of a pale brown semi-solid intermediate identified as precursor A. The reaction proceeded smoothly under controlled conditions, providing efficient conversion with minimal by-product formation.

Step 2: Formation of Intermediate B

Intermediate B was synthesized using ethyl chloroacetate and triethylamine in dichloromethane solvent. In this step, CuO nanoparticles acted as efficient heterogeneous nanocatalysts and facilitated electrophilic activation, nucleophilic substitution reactions, and enhanced reaction kinetics. The presence of CuO nanoparticles improved the reaction efficiency and selectivity while reducing overall reaction time. The catalytic surface of the nanoparticles provided active reaction sites, thereby promoting smooth conversion of the precursor into the desired intermediate.

Step 3: Formation of Intermediate D

The formation of intermediate D was carried out using sodium hydride in dimethylformamide (DMF) solvent under heating conditions at approximately 80°C. This step involved an important rearrangement reaction accompanied by carbon–carbon bond formation. The controlled reaction conditions enabled efficient structural transformation and stabilization of the intermediate compound necessary for subsequent heterocyclic modifications.

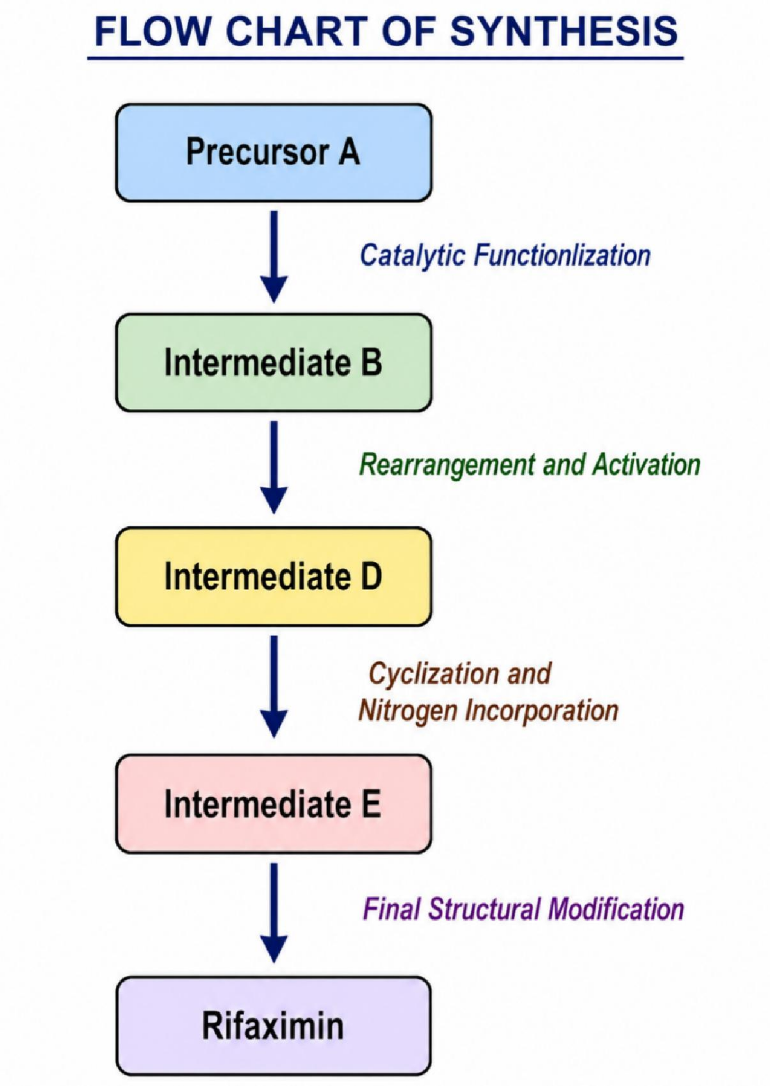
Step 4: Formation of Intermediate E

Intermediate E was synthesized by reacting the obtained intermediate with a hydrazine derivative in ethanol solvent under reflux conditions. CuO nanoparticles again played a significant catalytic role by promoting cyclization, nitrogen incorporation, and heterocyclic ring formation. The catalytic activity of CuO nanoparticles enhanced reaction efficiency and facilitated smooth formation of the heterocyclic intermediate under environmentally benign conditions.

Step 5: Final Formation of Rifaximin

The final step involved conversion of the intermediate into the rifaximin framework using phosphorus oxychloride ($POCl_3$) and triethylamine in toluene solvent. The reaction mixture was heated at approximately 110°C to facilitate completion of the transformation. Under these optimized conditions, the final rifaximin structure was successfully formed with good yield and purity. The developed synthetic methodology demonstrated improved reaction efficiency, operational simplicity, and environmentally sustainable pharmaceutical synthesis through the incorporation of green nanocatalytic principles.

IV. STEPWISE SYNTHESIS OF RIFAXIMIN



V. OBSERVATION TABLE

Step	Reaction Stage	Yield (%)	Observation
1	Precursor A formation	82	Pale brown semi-solid
2	Catalytic activation	—	Black suspension formed
3	Intermediate B	78	Orange crystals obtained
4	Intermediate D	80	Reddish-brown intermediate
5	Intermediate E	86	Brown crystalline solid
6	Final rifaximin synthesis	85–88	Reddish-orange crystals

CHARACTERIZATION OF RIFAXIMIN

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