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BIOSYNTHESIZED ZnO NANOPARTICLES FROM *Rumex nepalensis* (SPRENG.) PLANT EXTRACT SERVE AS EFFICIENT CATALYSTS FOR THE AQUEOUS SYNTHESIS OF 4H-ISOXAZOL-5-ONE DERIVATIVES

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ABSTRACT
In this study, the biosynthesis of ZnO nanoparticles was accomplished using an aqueous extract derived from Rumex nepalensis (Spreng) plant. The application of these biosynthesized ZnO nanoparticles as catalysts was investigated for the synthesis of biologically active 4H-isoxazol-5-one-based heterocycles. This was achieved through a one-pot three-component reaction involving hydroxylamine hydrochloride, aryl or heteroaryl aldehydes, and ethyl acetoacetate. The reactions were conducted at room temperature in aqueous medium, employing a 10 mol% loading of the biosynthesized ZnO catalyst. The structure of the biosynthesized ZnO was characterized using X-ray diffraction and scanning electron microscopy analyses. The resulting condensation process using biosynthesized ZnO nanoparticles exhibited environmentally friendly features such as safety, high yield of products, good atom efficiency, low cost, mild reaction conditions, minimal waste generation, avoidance of hazardous organic solvents, catalyst recoverability, energy efficiency, and facile workup.

INTRODUCTION

Green chemistry offers substantial benefits by minimizing the environmental impact of chemical processes. By reducing the use of hazardous reagents and solvents, green chemistry promotes sustainability and mitigates the release of toxic substances into the environment. The synthesis of green NPs aligns with these principles, making it an exciting area of research (Jadoun *et al*., 2021). Nanoparticles possess a large surface area and numerous active sites, making them highly effective catalysts for organic synthesis.

Nanoparticle-catalyzed reactions offer advantages such as high atom efficiency, mild reaction conditions, simplified product isolation, and easy recovery and recyclability of the catalysts. However, traditional chemical methods for nanoparticle synthesis involve harsh conditions and hazardous chemicals, making them expensive and environmentally unfriendly. In contrast, biosynthesis using microorganisms, enzymes, or plant extracts as reducing and stabilizing agents has gained attention for its eco-friendliness and cost-effectiveness (Krishnaraj *et al*., 2010).Plant-mediated synthesis, in particular, shows promise as a safe and viable alternative for large-scale production of metal nanoparticles (Zhan *et al*.,2011;Sheikh *et al*.,2022; Mungole *et al*.,2021; Chouke *et al*.,2021). Nanoparticles has been synthesized and evaluated for their several properties and applications by many workers to prove its signifacances (Bhokare *et al*., 2019, Choudhary *et al*., 2017, Sathya and Mahimairaja, 2018). Recent years have witnessed the impressive ability of plant extracts to convert metal ions into their nano-state, further supporting the viability of this approach.

Now a days, biosynthesis of metallic and metal oxide nanoparticles have been a subject of great interest among scientists for their remarkable chemical, physical, and biological properties.Presently nanoparticles of various metals using different plants are synthesized with different goals (Dandapat *et al.,* 2023; Sheikh *et al.,* 2023., Padhiary *et al*.,2023).

Biosynthesized Zinc oxide nanoparticles stand out as crucial players in various research fields, offering tremendous applications. They find use in textile industries (Huang *et al*.,2021), food packing (Kim *et al*.,2022), paints (Mani *et al*.,2022),antifungal(Mohamed *et al*., 2021). Moreover,Zinc oxide NPs are applied in medical field (Chinnapaiyan *et al*.,2022) and various environmental applications (Faisal *et al*.,2021).Also they serve as catalysts in chemical reactions (khan *et al*.,2021).The unique properties of ZnO NPs make them highly effective in promoting various chemical transformations and facilitating reactions. Their catalytic activity has been widely explored and documented in scientific literature (Fardood *et al*., 2019), (Hamedani *et al*., 2020). This

highlights the versatility of ZnO NPs not only as functional materials but also as catalysts, further contributing to their significance in the field of chemistry. Multicomponent reactions (MCRs) are powerful synthetic methods that involve the simultaneous reaction of three or more reactants to form a single product. They offer efficient and highly convergent approaches to construct complex molecular structures in a single step. MCRs have gained significant attention in organic synthesis and medicinal chemistry, due to their ability to rapidly generate diverse libraries of compounds. These reactions exhibit remarkable advantages, including high atom economy, speed, efficiency, and environmental friendliness. Due to these significant features, the development and refinement of new MCRs with environmentally benign protocols have become key topics in synthetic organic chemistry. MCRs streamline the synthetic process, allowing for the creation of diverse compound libraries, making them attractive for drug discovery and materials science. Their efficient and sustainable nature positions MCRs as essential methods in modern synthetic chemistry.

Zinc oxide nanoparticles have garnered significant interest as catalysts in various organic transformations due to their exceptional properties, including cost-effectiveness and ease of preparation. The biosynthesis approach presented in the research offers an eco-friendly alternative for the production of ZnO NPs, utilizing plant extracts as reducing and stabilizing agents. This method provides a viable and sustainable route for obtaining ZnO NPs with potential applications in diverse organic reactions (Soliman *et al.*,2020, Phukan *et al.*,2020,Satish kumar *et al.*,2019). Despite the widespread use of zinc oxide nanoparticles (ZnO NPs) in various applications, their potential for the synthesis of 4H-isoxazol-5-one compounds has not been explored. Considering the synthetic significance of these biologically relevant heterocyclic scaffolds and the known efficacy of ZnO NPs, this methodology has been applied, which offers mild reaction conditions and operational simplicity, for the synthesis of 4H-isoxazol-5-one derivatives.

The synthesis of heterocyclic systems containing an isoxazol ring holds significant importance in the fields of pharmaceutical chemistry and organic synthesis. One highly effective approach for constructing these systems is through the utilization of Multicomponent Reactions (MCRs). Isoxazol-based compounds, characterized by their five-membered heterocyclic structure, exhibit diverse biological activities and serve as valuable medicinal agents. They possess various therapeutic properties, including antiviral (Christodoulou *et al.*,2020), antifungal (Ali *et al.*,2022), antimicrobial (Mishra *et al.*,2022), anticancer (Faramarzi *et al.*,2023), anti-inflammatory (Pandhurnekar *et al.*,2021), antioxidant (Deshmukh *et al.*,2022) and COX-2 inhibitory (Cordero *et al.*,2020) activities. Moreover, the isoxazol core can be employed in the development of merocyanine dyes (Kulkarni *et al.*,2021),which find applications in optical recording and nonlinear optical research.

In this approach, ZnO NPs were utilized as efficient and reusable catalysts, and water was employed as the solvent (as depicted in Fig.1). This innovative strategy provides a promising avenue for the synthesis of 4H-isoxazol-5-ones, offering advantages such as the use of a green catalyst, mild reaction conditions, and the potential for catalyst recyclability. Therefore, the synthesis of isoxazole compounds is of great interest and significance in scientific research and medicinal formulations. In the above framework, this paper is deals with biosynthesis of ZnO nanoparticles from Rumex nepalensis (Spreng.) plant extract that is serving as efficient catalysts for the aqueous synthesis of 4H-isoxazol-5-one derivatives was taken into experimentation.

MATERIALS AND METHODS

Chemicals and materials

In this study, all the starting materials and solvents were obtained from commercial sources and used as received without undergoing additional purification. Melting points of the synthesized compounds were determined using an electro thermal melting point apparatus and were reported without any corrections. The progress of reactions was monitored using thin-layer chromatography (TLC) and visualized under UV light. The characterized products were identified by comparing their physical data, such as melting points, with those of known reference samples.

Preparation of Aqueous plant extracts

Aqueous plant extract was prepared by combining 20 g of powdered dried Rumex nepalensis (spreng) plant with 200 mL of water in a round-bottom flask. The mixture was heated to a temperature range of 60-70 ºC and boiled for a minimum of 30 minutes. After cooling to room temperature, the extract was filtered through Whatman No. 41 filter paper. The resulting boiled extract was refrigerated and utilized for subsequent experimental procedures.

Preparation of catalyst

The catalyst, zinc oxide nanoparticles (ZnO NPs), was prepared following previously reported protocol (Nava *et al.*, 2017).In a round-bottom flask (RBF), 100 mL of the extract obtained from Rumex nepalensis (spreng) plant was heated using a magnetic stirrer at a temperature range of 70-80 ºC. Subsequently, under constant stirring, 30 mL of an aqueous solution containing 3 g of zinc nitrate hexahydrate was added. The resulting mixture was boiled until a greenish-colored glue-like substance was obtained. This glue was collected and transferred into a ceramic crucible. The collected material was then calcined in a furnace at 500ºC for 2 hours. The final product obtained was black-colored, consisting of fine particles of ZnO NPs, which were subsequently used for characterization purposes.

General procedure for preparation of 4H-ISOXAZOL-5-ONES derivatives

The general procedure for the synthesis of 4H-isoxazol-5-one derivatives involved the following steps. Ethyl acetoacetate (1 mmol), aryl or heteroaryl aldehyde (1 mmol), hydroxylamine hydrochloride (1 mmol), and 10 mol% of biosynthesized ZnO nanoparticles were mixed in distilled water in a Schlenk tube. The reaction mixture was stirred at room temperature. The progress of the reaction was monitored using TLC analysis, and the required time for completion was recorded (Table 3).Upon completion of the reaction, the reaction mixture was filtered, and the residue was dissolved in hot ethanol. Filtration

was performed again to separate the product as the filtrate from the catalyst. The same catalyst was reused for the synthesis of further derivatives. The product was obtained by allowing the filtrate to cool, and recrystallization from hot ethanol was conducted to yield pure desired compounds in high yields. The identity of known products was confirmed by comparing their physical data with those previously reported in recent literatures [as depicted in Table 3].

RESULTS AND DISCUSSION

EIn the initial experiments, the nanoparticle was subjected to characterization using X-ray diffraction (XRD) and scanning electron microscopy (SEM) analysis. XRD analysis provided information about the crystal structure of the nanoparticles, while SEM analysis offered insights into their morphology and surface features. These characterization techniques allowed us to gain a better understanding of the structural and morphological properties of the synthesized nanoparticles.

The biosynthesized zinc oxide nanoparticles (ZnO NPs) were subjected to X-ray diffraction (XRD) analysis to determine their crystalline structure (Fig.1a). The XRD pattern exhibited diffraction peaks that corresponded precisely to the hexagonal wurtzite structure of ZnO NPs (JCPDS card no: 01–089–1397) (Dappula *et al*., 2023). This indicates that the biosynthesized ZnO NPs possess a well-defined and consistent hexagonal wurtzite crystal structure, characterized by specific lattice parameters. The size of the ZnO nanoparticles was determined using the Debye-Scherrer equation (D = K*ë*/*â*cos*è*), where D represents the average crystallite size diameter. By applying this equation with a shape factor (K) of approximately 0.9, an X-ray wavelength (*ë*) of 1.5406 Å for Cu K*á*, and diffraction peak position (*è*), the calculated average crystallite size of the ZnO NPs was found to be 20.7903 nm.

SEM analysis displayed predominantly spherical morphology of the biosynthesized ZnO nanoparticles (NPs), as shown in Fig.1b.

After characterization of biosynthesized ZnO NPs, Initially, model reaction was performed using multi-component condensation reaction of m-hyroxyl-benzaldehyde, hydroxylamine hydrochloride, ethyl acetoacetate and water as solvent in the in the presence of biosynthesized ZnO NPs (Fig.2) to optimize the reaction conditions. In the initial stages of this work, a comparative study was conducted to assess the catalytic efficiency of biosynthesized ZnO NPs in comparison to other catalysts in study shown in the Table 1. The results revealed that biosynthesized ZnO NPs demonstrated superior activity, leading to a high yield of the desired product. This enhanced catalytic performance of biosynthesized ZnO NPs is attributed to its larger surface area, which facilitates increased

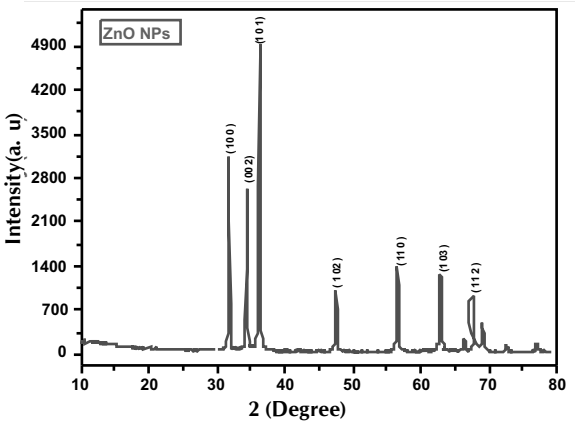


Figure: 1a) XRD pattern of ZnO NPs analyzed

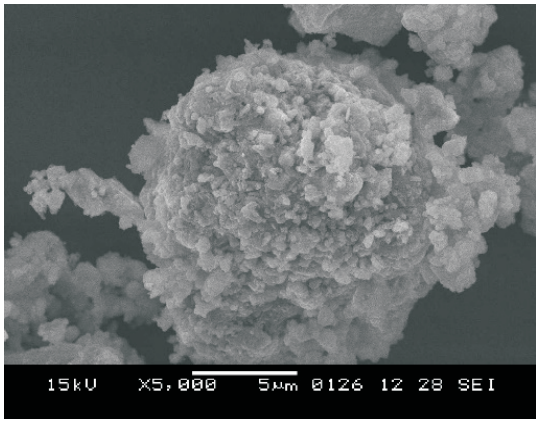


Figure: b) SEM image of ZnO NPs visualized.

Table 1: Study for synthesis of 4H-isoxazol-5-ones derivatives in the presence of various catalysts

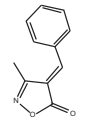
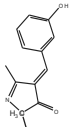
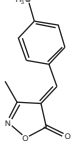
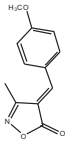
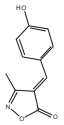
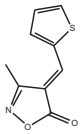
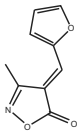
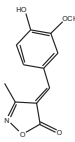
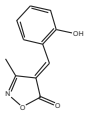
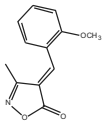
Sr. no.	Catalyst	Mol% (Conditions)	Time	% Yields	References
1	Salicylic acid	15 (Water, R.T)	75	92	(Mosallanezhad *et al*., 2019)
2	Guanidine hydrochloride	15 (Water, R.T)	60	90	(Barkule *et al*., 2022)
3	Pyridine	100 (Reflux)	60	77	(Ablajan *et al*., 2011)
4	Sodium benzoate	10 (Water, R.T)	90	88	(Liu *et al*., 2011)
5	Catalyst free	(Water, R.T)	120	91	(Chavan *et al*., 2015)
6	Antimony trichloride	22 (Water, R.T)	165	85	(Pourmousavi *et al*., 2018)
7	Potassium carbonate	5(Water,Reflux)	150	80	(Laroum *et al*., 2019)
8	Biosynthesized ZnO NPs	10 (Water, R.T)	75	94	Present work

Table 2 : Model reaction using different solvents.

Sr. no.	Solvent	Catalyst (Mol %)	Time (Min)	% Yields[a]
1	n-hexane	10	75	25
2	Acetone	10	75	30
3	Ethanol	10	75	80
4	Methanol	10	75	70
5	Water	5	75	85
6[b]	Water	10	75	94, 94,93
7	Water	15	75	93
8	Water	20	75	92
9	water	25	75	92

[a]Isolated yields [b]Catalyst was reused three times.

Table 3 : Synthesis of 4H-isoazol-5-onesderivatives using catalyst biosynthesized ZnO NPs in the presence of aqueous medium

Entry	Aryl or Hetero -aryl aldehyde	Desired products	Time (Min)	% Yield	M.P (^{0}C) Observed	References
1	C_6H_5CHO **1a**	 **4a**	70	92	142–143	141–143 (Liu *et al.*,2012)
2	m-OHC_6H_4CHO **2b**	 **4b**	75	94	201-203	202 – 203 (Safari *et al.*,2016)
3	p-MeC_6H_4CHO **3c**	 **4c**	60	95	130 -132	129 -131 (Bashash *et al.*,2016)
4	p-$OMeC_6H_4CHO$ **4d**	 **4d**	60	94	174 - 176	173 -175 (Kalhor *et al.*,2020)
5	p-OHC_6H_4CHO **5e**	 **4e**	60	95	214 – 215	212 – 215 (Khandebharad *et al.*,2015)
6	C_4H_3SCHO **6f**	 **4f**	50	93	143–144	140–143 (Farahi *et al.*,2018)
7	C_4H_3OCHO **7g**	 **4g**	65	93	240–242	238–241 (Setamdideh *et al.*,2015)
8	p-$OHC_8H_7O_2CHO$ **10h**	 **4h**	75	94	212–215	211–214 (Kiyani & Samimi *et al.*,2017)
9	o-OHC_6H_4CHO **11i**	 **4i**	90	86	196 - 198	195 – 197 (Kalhor *et al.*, 2021)
10	o-OMe-C_6H_4 **12j**	 **4j**	55	94	161 -163	162 -164 Mirzazadeh *et al.*, 2012)

adsorption of reactants on its surface. Encouraged by these findings, biosynthesized ZnO NPs nanoparticles were employed instead of bulk biosynthesized ZnO NPs in subsequent test reactions. The use of biosynthesized ZnO nanoparticles significantly reduced the reaction time. The higher surface area and improved dispersion of the nanoparticles in the reaction mixture are believed to be responsible for the enhanced catalytic activities of biosynthesized ZnO NPs.

In the subsequent stages, the optimization of catalyst amounts was performed in the Model study, employing various quantities of ZnO NPs. The highest yield was achieved when the catalyst amount was increased from 5 mol% to 10 mol%. However, further elevating the molar amount of the catalyst from 10 mol% to 25 mol% did not result in a substantial increase in the product yield. (Fig.2a).Consequently, the optimum concentration of ZnO NPs was determined to be 10 mol % for the model reaction. Optimization reactions were carried out at room temperature in aqueous medium.

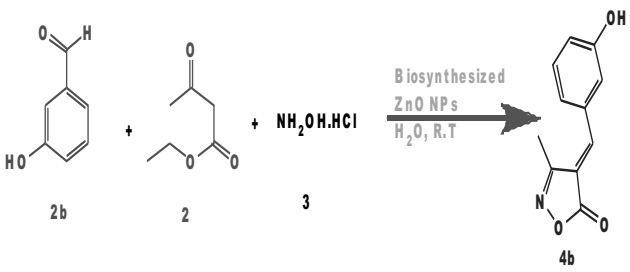


Fig ure 2: Model reaction using catalyst biosynthesized ZnO NPs for the synthesis of 4H-isoxazole-5-one derivatives.

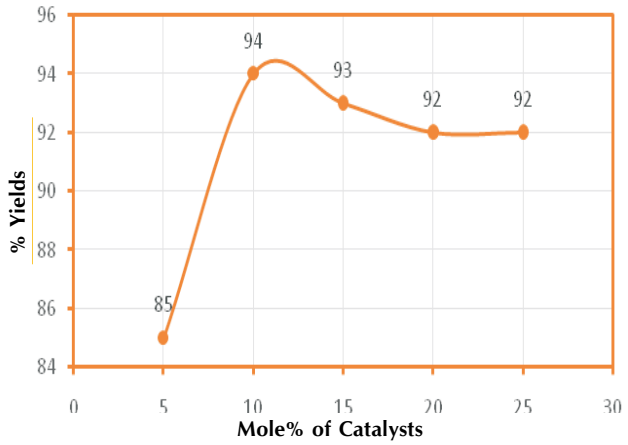


Fig.2a). Effect of catalyst amount on the model reaction's outcome.

To enhance the yield of the desired product, we examined the impact of different solvents in the model reaction, and the results are presented in Table 2. The findings demonstrate that using water as the solvent significantly accelerated the reaction rate, resulting in high yields for all products. This indicates that the presence of water as a solvent facilitated efficient interactions between the reactants and the catalyst, leading to improved reaction kinetics and enhanced product formation.

After optimizing the reaction conditions, we conducted the reaction of substituted aromatic aldehyde, ethyl acetoacetate, hydroxylamine hydrochloride using 10 mol % ZnO NPs in aqueous medium. A series of experiments yielded 4H-isoxazol-5-ones derivatives in excellent yields and a short reaction time.

In numerous investigations carried out by multiple researchers, it has been ascertained that a wide range of substituted benzaldehydes, incorporating electron-donating groups on the phenyl ring, lead to the formation of the respective heterocyclic products with notable efficacy and in considerable isolated yields (Kulkarni, 2021, Asadi *et al*., 2021, Kalhor *et al*.,2020, Barkule *et al*.,2022, Gadkari *et al*.,2020, Tajbakhsh *et al*.,2022).

This research work successfully prepared a small library of 4H-isoxazol-5-ones derivatives using biosynthesized Zinc oxide nanoparticles, as illustrated in Table 3. The presence of electron-donating groups, such as hydroxyl (-OH), methyl (-CH3), and methoxy (-OCH3), on the phenyl ring has been observed to positively impact reaction yields and times. These groups augment reactivity by donating electron density to the ring, thereby increasing its nucleophilicity. Consequently, reactions involving such electron-donating groups on the phenyl ring often yield products with high efficiency. However, in the case of hydroxyl-functionalized aromatic aldehydes, specifically o-hydroxybenzaldehyde, the reaction exhibits longer reaction times and lower yields of the desired product when compared to p-hydroxybenzaldehyde and m-hydroxybenzaldehyde. This disparity can be attributed to steric crowding caused by the ortho-positioning of the hydroxyl group, which restricts the accessibility of the reactants and hampers the reaction efficiency (as indicated in Table 3).

Further exploration of the current reaction involved the utilization of electron-rich heterocyclic aryl aldehydes, specifically thiophene-2-carbaldehyde and furan-2-carbaldehyde. Remarkably, the results showed successful progression of the reaction with high yields and short reaction times in these instances (as shown in Table 3). This outcome further emphasizes the significance of electron-rich substituents in promoting efficient reactions and underscores their potential utility in the synthesis of valuable heterocyclic compounds.

Previous studies by various researchers on nanoparticle-catalyzed reactions supported this investigation. Such as, Magnesium oxide nanoparticles effectively catalyzed a three-component reaction, yielding biologically active isoxazole-5(4H)-one-based heterocycles. Environmentally friendly heterocyclization offers safety, low cost, high yield, minimal waste, energy efficiency, mild conditions, good atom efficiency, catalyst recoverability, and avoids hazardous solvents (Kiyani and Ghorbani, 2016), An eco-friendly method using ZnO@Fe3O4 core-shell nanocatalyst was developed for synthesizing isoxazol-5(4H)-one derivatives. The one-pot reaction of aldehydes, hydroxylamine hydrochloride, and ethyl acetoacetate in water at slightly elevated temperature provided high yields of title compounds. The approach offers safety, atom efficiency, low cost, minimal waste, recyclable catalyst, and excellent functional group tolerance for diverse isoxazole derivatives (Shanshak *et al*., 2020), An eco-friendly method using GO@Fe(ClO4)3 nanocatalyst for synthesizing isoxazol-5(4H)-one derivatives was proposed. The one-pot reaction of aldehydes, hydroxylamine hydrochloride, and ethyl acetoacetate under solvent-free conditions at 100ºC provided 4-(arylmethylidene)-3-methyl-1,2-oxazol-5(4H)-ones in good to excellent yields. This approach offers safety, atom efficiency, low cost, recyclable catalyst, and excellent functional group tolerance for diverse isoxazole derivatives (Madandar *et al*., 2022). Method for one-pot synthesis of 3-methyl-4-(phenyl)methylene-isoxazole-5(4H)-one derivatives using acid-functionalized Fe3O4 nanoparticles as a catalyst. Ultrasound energy facilitated catalyst preparation and compound synthesis. The protocol offers mild conditions, easy catalyst recovery, short reaction time, and the use of environmentally friendly solvents (Nongrum *et al*.,2023).Therefore, the importance and utility of 4H-isoxazol-5-one derivatives are vast and multifaceted.

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