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MICROWAVE ASSISTED SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF NEWLY SYNTHESIZED 1, 3, 4-THIADIAZOLE DERIVATIVE OF GUAR GUM

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Keywords:

Guar Gum, 1, 3, 4-thiadiazole, Antioxidant activity, Hydrogen peroxide scavenging activity, Antimicrobial activity

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ABSTRACT: A new derivative of Guar gum, incorporated with 1, 3, 4-thiadiazole nucleus was synthesized by using a new green and efficient synthetic approach. Guar gum is a biodegradable polymer having numerous applications in various industries. Thiadiazole compounds are well known in the therapeutic world due to their pharmacological importance. The newly synthesized derivative was characterized by IR, H^1 NMR, and mass spectrometry. Its antioxidant activity was determined by hydrogen peroxide scavenging activity. Its antimicrobial activity was also studied.

INTRODUCTION: Green color signals to proceed and green chemistry signals to sustain. In the present study, a significant greener approach of synthesis, *i.e.*, microwave assisted synthesis is used to synthesize a novel derivative. Microwave irradiation assisted chemical transformations are pollution free, quicker, eco-friendly and offer high yield together with simplicity in processing and handling [1]. Guar gum (*Cyamopsis tetragonoloba*) represents Galactomannan family of poly-saccharides. It is a nontoxic, biodegradable natural polymer by modifying rheological properties. Although this is easily available at a low cost, but its uncontrolled hydration upon storage and further microbial contamination limit its long term application.

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Chemical modification of Guar gum diversifies and enhances its applications and functionality [2-3]. Here we have incorporated a therapeutically important heterocyclic nucleus 1, 3, 4- thiadiazole in Guar gum.

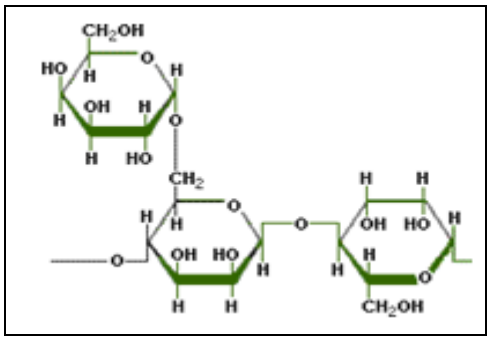


FIG. 1: GUAR GUM STRUCTURE

1, 3, 4-thiadiazole has gained significant attention due to its diverse range of biological properties. This heterocyclic nucleus exhibited remarkable pharmacological activities such as anti-inflam-matory, anticancer, antimicrobial, antioxidant, anti-anxiety, analgesic, diuretic, antidiabetic due to the presence of N=C-S moiety and strong aromaticity

of the ring which leads to greater *in-vivo* stability and lesser toxicity. So when this thiadiazole moiety is attached with natural polymer Guar then compound containing outstanding antimicrobial and antioxidant properties are obtained [4-5].

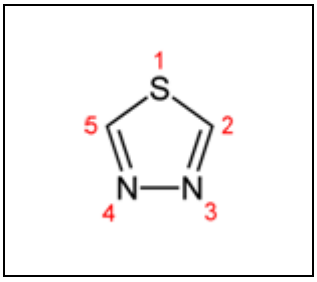


FIG. 2: 1, 3, 4-THIADIAZOLE

Materials: Guar (200 mesh size) was procured from local industry. All AR grade chemicals used were procured from Sigma Aldrich, Loba Chemicals, and Ases chemical works. The bacterial and fungal strains used for evaluation of antimicrobial activities were obtained from S. N. Medical College, Jodhpur.

Methods:

Synthesis of Epoxy Ether of Guar: One mole of guarana powder was slurred in DMSO solvent in a round bottom flask. Then 50% aqueous NaOH was added in the slurry to make the reaction mixture alkaline, and the mixture was constantly magnetically stirred at 45 °C for 2 h. Further 1 mole of epichlorohydrin was added gradually with continuous stirring, and the pH was adjusted to 9-10 then this reaction mixture was subjected to microwave for 15 min. Later, the compound was filtered on vacuum pump with 80% aqueous methanol containing few drops of nitric acid to remove inorganic impurities of chloride ion and excess of alkali [6].

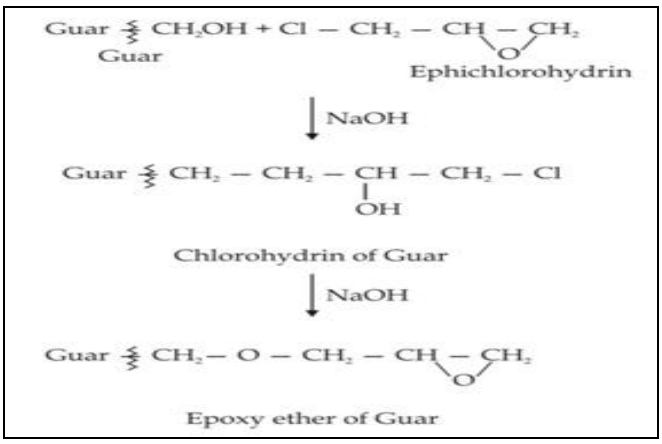


FIG. 3: SYNTHESIS OF EPOXY ETHER OF GUAR

Synthesis of 5-(arylamino)- 2-sulfanyl 1, 3, 4-thiadiazole: 0.1 moles of aniline was dissolved in 20 ml of ammonia solution to which 0.1 moles of carbon disulphide was gradually added with constant stirring. The temperature of the solution was kept below 30 °C. 20-25 ml of ethanol was then added, and the stirring was continued till all the carbon disulphide dissolved. The reaction mixture was then allowed to stand for 2 h.

An equimolar quantity of sodium hydroxide and monochloroacetic acid were taken, dissolved separately in water and cooled. After cooling, mix the solutions to obtain sodium salt. This sodium chloroacetate solution was added to the reaction mixture followed by the addition of 10 ml of 50% hydrazine hydrate. The mixture became warm; it was cooled, filtered, dried and recrystallized with ethanol [7].

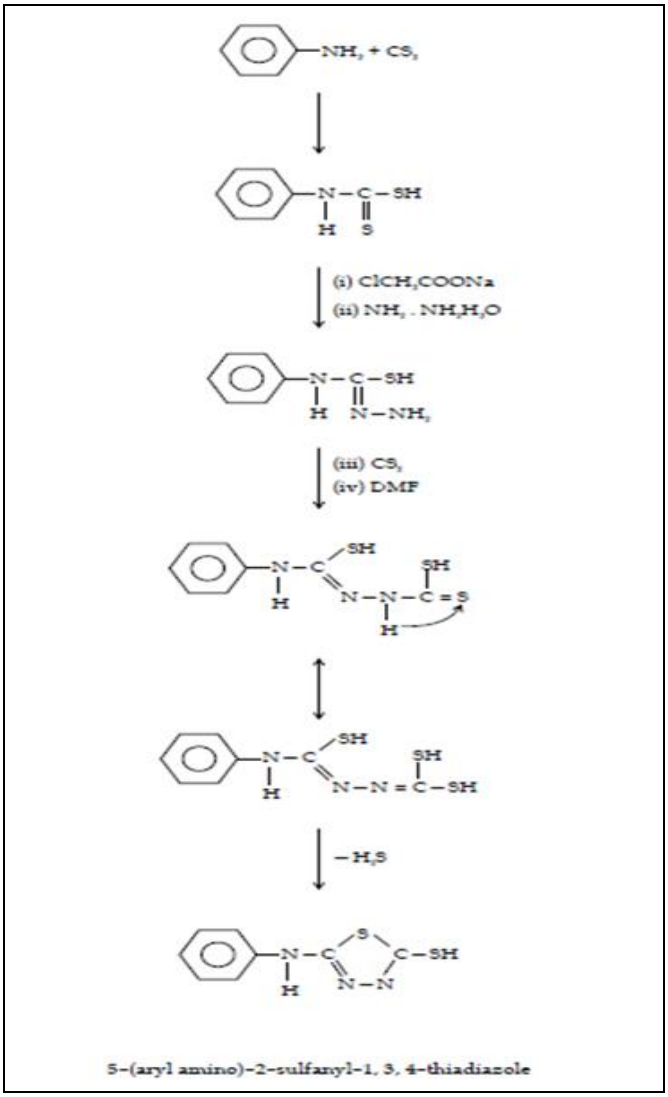


FIG. 4: SYNTHESIS OF 5-(ARYL AMINO) - 2-SULFANYL 1, 3, 4- THIADIAZOL

Synthesis of 5-(N-Guar epoxy aryl amino)-2-(mercapto carboxy methyl- N- methyl piperazine)-1, 3, 4-thiadiazole: In a reaction vessel equimolar quantities of 5-(arylamino)-2-sulfanyl 1, 3, 4-thiadiazole and chloro acetyl chloride is taken. To this N-methyl piperazine was added and irradiated it with microwaves for 10-12 min. The solution was then filtered, and the precipitate was then dried. The derivative formed is mixed with 1, 2 epoxy propyl guar in a beaker by adding a minimum quantity of DMSO. This reaction mixture was then place in the microwave for 15 min. The solution was then filtered and the precipitate was then washed with methanol. Later it was dried and weighed.

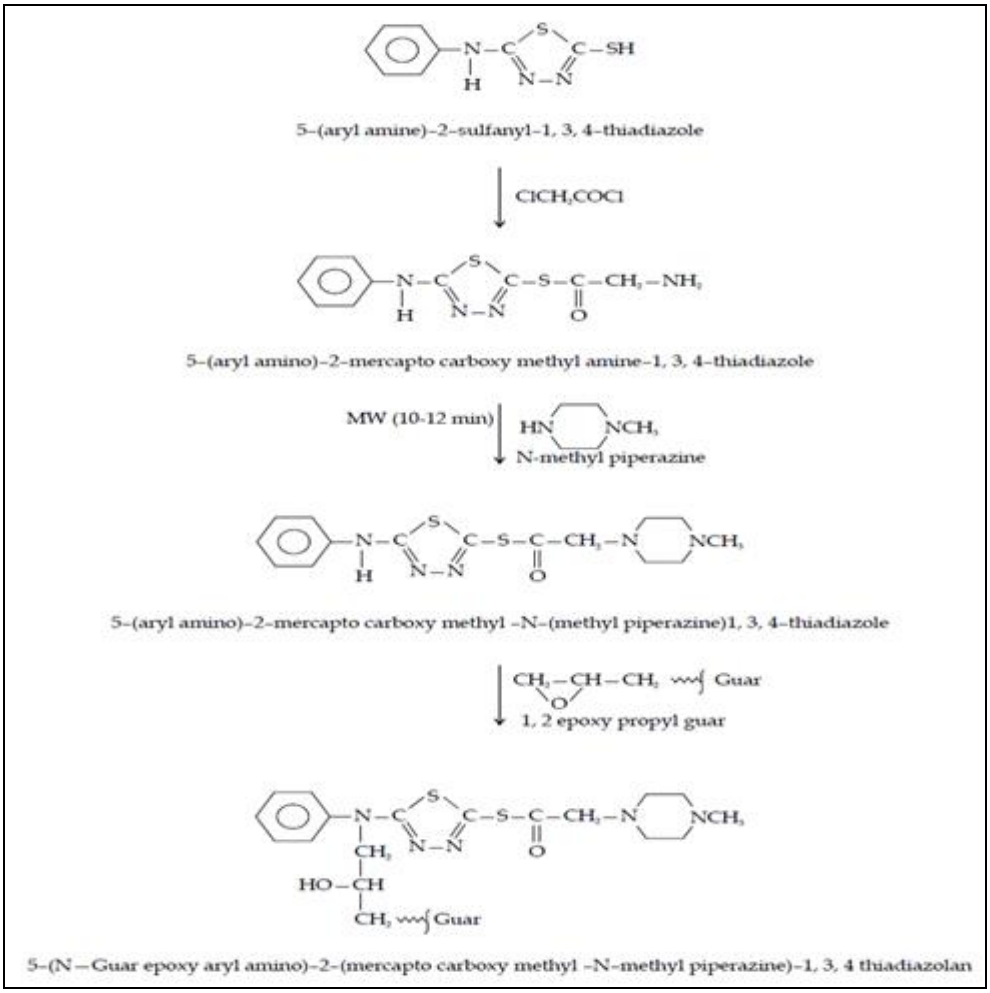


FIG. 5: SYNTHESIS OF 5-(N-GUAR EPOXY ARYL AMINO)-2-(MERCAPTO CARBOXY-N-METHYL PIPERAZINE)-1, 3, 4-THIADIAZOLE

Characterization: Melting point of the compound is determined in open capillary tube and is uncorrected. The newly formed derivative was characterized by FTIR spectroscopy, H^1 NMR Spectroscopy, Mass spectrometry, elemental analysis.

Antimicrobial Activity: An antimicrobial agent has the capability of destroying or inhibiting any disease-causing microbes. It can be a chemical, or a physical agent. 1, 3, 4 thiadiazole is an important scaffold known to be associated with several biological activities. It can act as a bio-isosteric replacement of the thiazole moiety. So it can act like 3rd and 4th generation of cephalosporins, hence can be used in antibiotic preparation. The newly synthesized compound was screened for its antibacterial and antifungal activities against *Escherichia coli, Klebsiella pneumonia*, *Staphylococcus aureus,* Coagulase-negative *staphylococci* (CONS), C*andida albicans* and *Candida parapsilosis.*

A pure isolate of each bacterium and fungi are the first subcultured in nutrient broth at 37 °C for 24 h and 48 h respectively. Then these were mixed with

sterile physiological saline (0.9%), and the turbidity was adjusted to the standard inoculums of Mc Farland scale (0.5 for bacteria and 2.0 for fungi). The inoculums were spread on the surface of the solidified media. Wells of approx 6 mm were dig on the sterile agar plate, and solution of the derivative is filled in a well. DMSO was used as the solvent for the compounds. A blank test was carried out to check the antimicrobial activity of DMSO. Standard drugs, ampicillin for bacteria and fluconazole for fungi were used. Plates were incubated for 1-2 days. Zones of inhibition were measured [8-11].

Antioxidant Activity: Antioxidants are compounds capable to either delay or inhibit the oxidation processes which occur under the influence of atmospheric oxygen or reactive oxygen species. They are involved in the defense mechanism of the organism against the pathologies associated with the attack of free radicals. Free radicals are responsible for causing a large number of diseases including cancer, neural disorders, Parkinson's disease, and aging. Protection against free radicals can be enhanced by ample intake of dietary antioxidants.

In the present study, the antioxidant activity of newly synthesized derivative is analyzed by H_2O_2 scavenging assay [12-14].

Hydrogen Peroxide Scavenging Assay: The ability of the newly synthesized derivative to scavenge Hydrogen peroxide was estimated according to the method of Ruch *et al*., (1989) [15]. A solution of hydrogen peroxide (40 mM) was prepared in phosphate buffer (50 mM, pH -7.4). A test sample solution in DMSO is added to hydrogen peroxide, and the absorbance at 230 nm is determined after every 10 min against a blank solution containing phosphate buffer without hydrogen peroxide. The percentage of H_2O_2 scavenging is calculated as follows:

$$\% \text{ scavenged } (H_2O_2) = [(A_i - A_t / A_i)] \times 100$$

Ai = absorbance of control
A_t = absorbance of the test sample

RESULTS AND DISCUSSIONS: Spectral characterization data of the compound suggest the structure of the compound.

FT-IR Analysis: IR Spectra was recorded with BRUKER spectrophotometer. The spectrum of the newly synthesized compound shows a peak at 1037.29 cm^{-1} represents C-O stretching. The peak at 1513.42 cm^{-1} is due to C-S stretching. The peak at 1706.07 cm^{-1} is due to N-H bending. Peaks at 2366.14 cm^{-1} and 3742.92 cm^{-1} show C=N stretching and –OH stretching respectively **Fig. 6**.

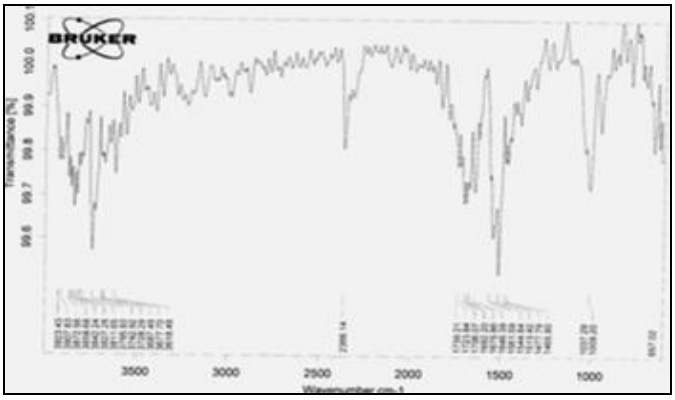


FIG. 6: IR SPECTRA

Mass Spectral Analysis: DART-MS was recorded on a JEOL-AccuTOF JMS-T1OOLC Mass spectrometer having a DART (Direct analysis in real time) source. The compound was subjected as such in front of DART source. Dry Helium was used with 4 LPM flow rate for ionization at 350 °C. The orifice 1 was set at 28 V. Mass spectral analysis- Base peak at 157.07 **Fig. 7**.

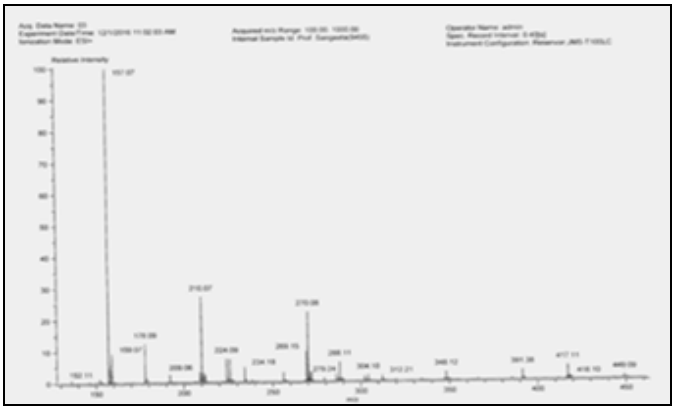


FIG. 7: MASS SPECTRA

H^1 NMR Analysis: NMR Spectra was determined by Bruker AV-II 300 MHz FT-NMR Spectrometer. The compound was dissolved in DMSO. The interpretation shows a peak at δ3.46 for aromatic amine proton (C_6H_5N-H). Other peaks at δ2.5 to 3.5 may be due to methylene protons, and the upfield signal at δ 7.35 is due to aromatic proton (Ar-H) **Fig. 8**.

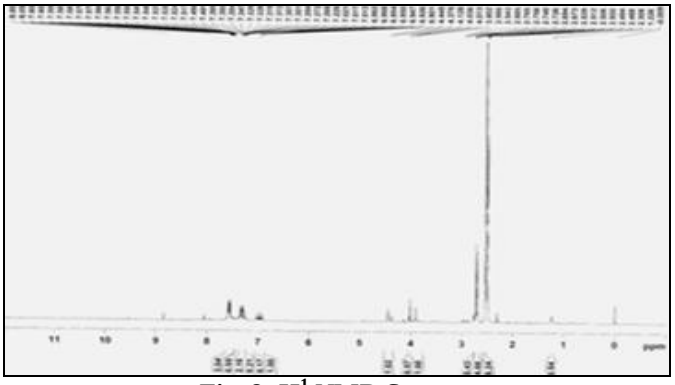


Fig. 8: H^1 NMR Spectra

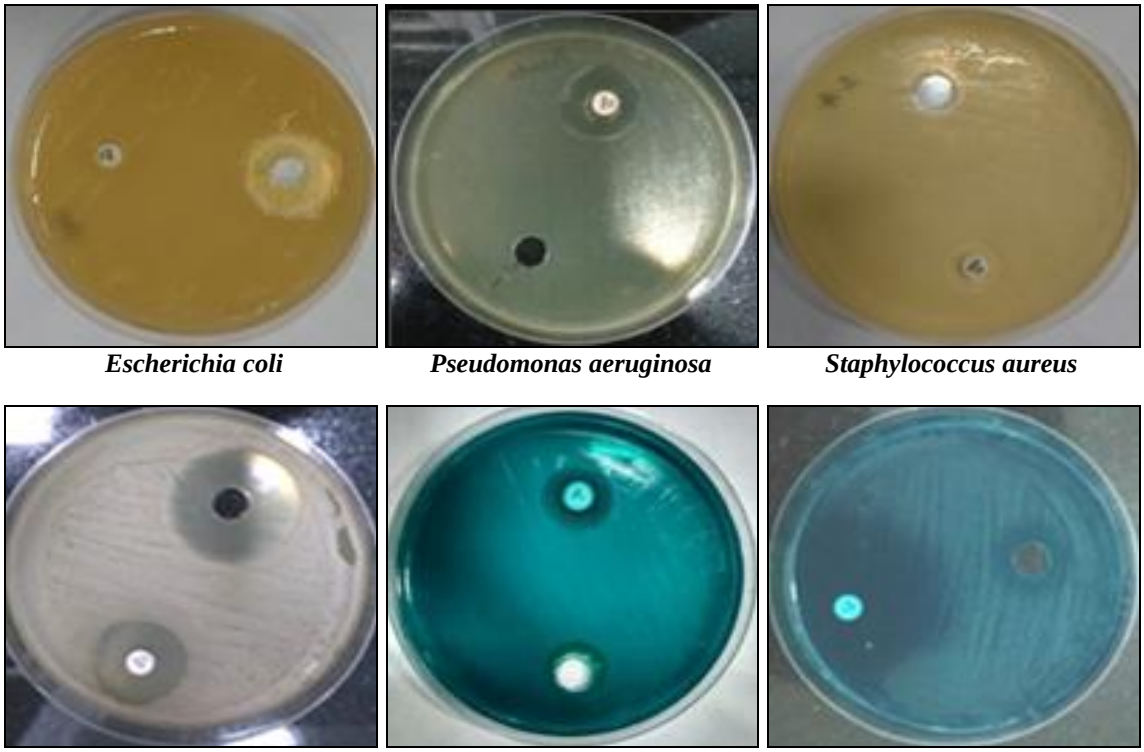
Antimicrobial Activity: From the antibacterial and antifungal screening, it was concluded that the compound was active against bacteria *Escherichia coli*, *Klebsiella pneumonia*, *Staphylococcus aureus*, Coagulase-negative *Staphylococci* (CONS), *Candida albicans*, *Candida tropicalis* **Table 1**.

TABLE 1: ANTIBACTERIAL ACTIVITY OF 1, 3, 4 THIADIAZOLE DERIVATIVE OF GUAR GUM

S. no.	Bacterial strains	Type	Zone of inhibition
1	*Escherichia coli*	Gram negative	05 mm
2	*Pseudomonas aeruginosa*	Gram negative	No
3	*Staphylococcus aureus*	Gram positive	04 mm
4	Coagulase negative *Staphylococci* (CONS)	Gram positive	07 mm

TABLE 2: ANTIFUNGAL ACTIVITY OF 1, 3, 4 THIADIAZOLE DERIVATIVE OF GUAR GUM

S. no.	Fungal Strains	Zone of Inhibition
1	*Candida albicans*	5 mm
2	*Candida tropicalis*	10 mm



Escherichia coli ***Pseudomonas aeruginosa*** ***Staphylococcus aureus***

Coagulase Negative *Staphylococci* ***Candida albicans*** ***Candida tropicalis***

FIG. 9: ANTIMICROBIAL ACTIVITY OF THE NEWLY SYNTHESIZED DERIVATIVE

Antioxidant Activity: The hydrogen peroxide scavenging activity shows that the oxidation power of the compound decreases with increase in time.

TABLE 3: ANTIOXIDANT ACTIVITY

S. no.	Time	Absorbance at 230 nm	% H_2O_2 Scavenging activity
1	0 min	0.1835	81.00%
2	10 min	0.2268	77.25%
3	20 min	0.2875	71.11%
4	30 min	0.3119	68.71%
5	40 min	0.4571	54.53%

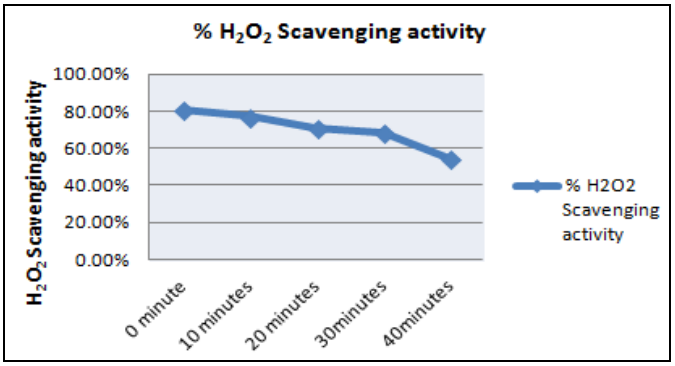


FIG. 10: H_2O_2 SCAVENGING ACTIVITY

CONCLUSION: Microwave assisted synthesis has now become an important part of the organic synthesis. The properties of the synthesized compound are superior to the compound that synthesized by heating method. The compound showed good antimicrobial and antioxidant properties. So there is ample scope to extend the applicability of this technique.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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