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Sustainable methods for producing food-derived bioactive compounds

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ABSTRACT

Background: Pursuing alternative starting materials has gained significant importance in the food and drug industries, driven by the global shift towards sustainable and renewable resources. Terpenes, naturally occurring hydrocarbons derived from plants, present a promising solution due to their abundant availability and range of physiological activities, including antioxidant, anti-inflammatory, antimicrobial, and anticancer properties.

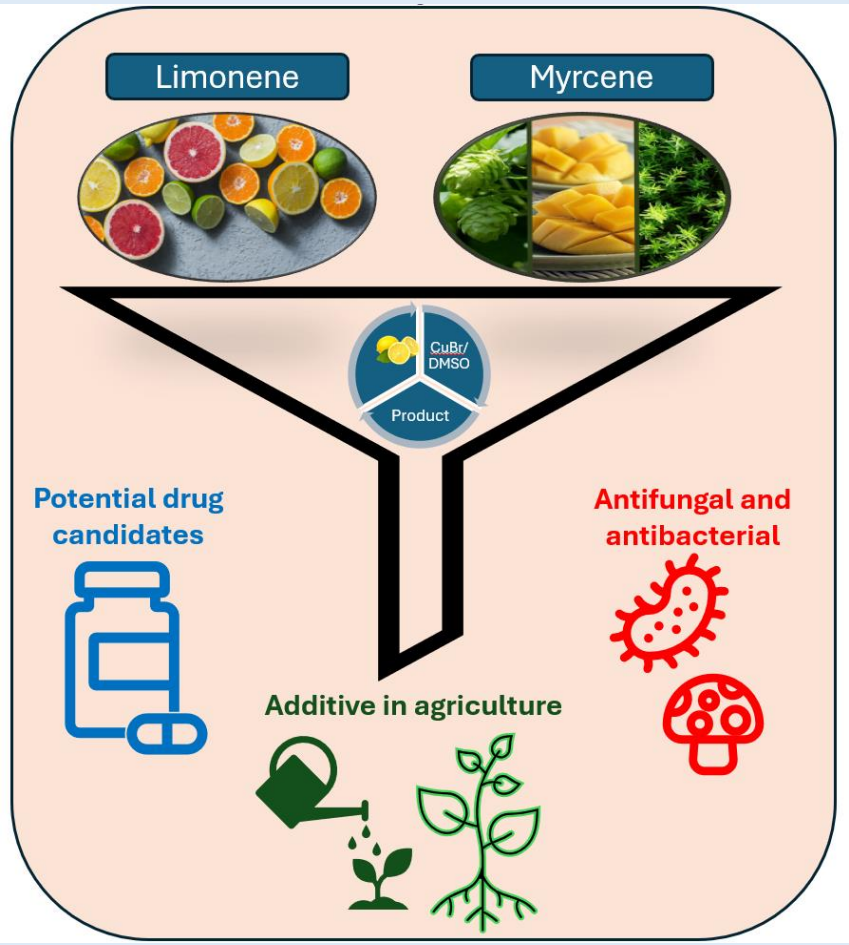
Objective: This study aims to develop a waste-free synthesis methodology for functionalizing limonene and myrcene, two notable terpenes, through Atom Transfer Radical Reactions (ATRR). The objective is to achieve high yields and purities while enhancing the therapeutic potential of these compounds and adhering to green chemistry principles.

Methods: A catalytic complex of Cu(I)Br and dimethyl sulfoxide (DMSO) was used to facilitate the coupling of limonene and myrcene with various trichloroacetic acid derivatives. Reactions were performed at 80°C for 90 minutes, and products were purified by column chromatography. The synthesized compounds were characterized using Gas Chromatography-Mass Spectrometry (GC-MS) and Nuclear Magnetic Resonance (NMR). Microbiological analyses were conducted using the disk-diffusion method, and statistical analyses were performed to assess the reliability of the experiments.

Results: The ATRR methodology enabled the efficient functionalization of limonene and myrcene, achieving high yields and purities. The best yield for limonene was 70%, and for myrcene, 82%, both using trichloroacetonitrile. The Cu(I) catalytic system showed dualistic biological effects, with 3% concentration exhibiting strong bactericidal and fungicidal activity, while 0.03% promoted growth. These results demonstrate the potential of the methodology and the catalytic system for bioactive compound synthesis and agricultural applications.

Conclusion: This study demonstrates the viability of ATRR for efficiently functionalizing limonene and myrcene, achieving high yields and purities. The synthesized compounds show promise for pharmaceutical development. The dual antibacterial and antifungal activities of the Cu(I) catalytic system also suggest potential applications in wastewater reutilization. Future work should explore the biological effects and environmental impact of this process.

Keywords: Terpenes, ATR reactions, Green Chemistry, Bioactive compounds, Therapeutic potential.



Graphical Abstract: Sustainable methods for producing food-derived bioactive compounds

INTRODUCTION

In recent years, the pursuit of alternative starting materials has gained high importance, particularly within the food and drug industries. The global shift towards sustainable and renewable resources underscores the necessity for finding viable replacements for traditional

chemical feedstocks. Terpenes, naturally occurring hydrocarbons derived from plants, present a promising solution. These compounds areabundantly available andexhibit a range of physiological activities, including antioxidant, anti-inflammatory, antimicrobial, and anticancer properties [1-5]. The inherent therapeutic potential of terpenes further amplifies their significance as alternative starting materials.

Among the vast array of terpenes, limonene, and myrcene stand out for their remarkable therapeutic potential. Limonene, commonly extracted from citrus fruits, has been extensively studied for its potent anti-inflammatory and anticancer effects [6-8]. Myrcene, found in hops and lemongrass, has garnered attention for its analgesic and sedative properties [9-11]. By harnessing these natural compounds as building blocks in synthetic chemistry, researchers can unlock new therapeutic possibilities while embracing sustainable development.

The synthesis of carbocycles, which form the backbone of many active pharmaceutical ingredients, is an area of significant interest in medicinal chemistry. The development of cost-effective, rapid, and accessible synthesis methods for these compounds is crucial. In this context, the concept of waste-free synthesis emerges as a pivotal objective. Terpenes such as limonene and myrcene are ideal candidates for the synthesis of carbocycles, offering a renewable and inexpensive starting material. Atom transfer radical addition (ATRA) and cyclization (ATRC) reactions present a robust synthetic strategy, enabling the functionalization of double bonds in terpenes through coupling with trichloroacetic acid derivatives [12-14]. This methodology is advantageous due to its efficiency, cost-effectiveness, and extensive scope for functionalization, including the potential to substitute chlorine atoms with amino groups to synthesize amino acid derivatives [15]. The resulting terpene-carbocycle molecules are anticipated to have considerable pharmacological value, merging the bioactive properties of both components. This innovative approach aligns with green chemistry principles, prioritizing environmentally benign processes, waste minimization, and economic viability. Utilizing wastewater to produce agrochemicals and plant nutrients exemplifies a circular economy in the chemical industry [16-17].

Therefore, the development of waste-free synthesis methodologies for potential bioactive compounds derived from natural sources is both valid and essential. Such approaches align with the principles of green chemistry and sustainability, offering a promising pathway to produce therapeutic agents with minimized environmental impact. By harnessing the inherent therapeutic potential of terpenes and employing innovative synthetic strategies, we can advance the field of medicinal chemistry toward more sustainable and effective solutions.

MATERIALS AND METHODS

Materials

All chemicals were purchased from VWR company:

- Limonene (≥95% for synthesis; VWR cat. #: 8.18407.0500)
- Myrcene (≥90% tech. stabilized; VWR cat. #: ACRO128080025)
- Dimethyl sulfoxide, DMSO (≥99.5% Ultra-Pure Grade; VWR cat. #: N182-5X10ML)
- Piperidine (≥99.5% GPR RECTAPUR®; VWR cat. #: 85981.290P)
- Trichloroacetic acid (≥99%, glacial Ph. Eur.; VWR cat. #: 20741.290)
- Trichloroacetonitrile (≥98%; VWR cat. #: A10565.0B)
- Ethyl trichloroacetate (≥99%; Sigma-Aldrich®; VWR cat. #: SIAL163155-100G)
- Sodium sulfite (anhydrous ≥98% ACS; VWR cat. #: 0628-1KG)
- Sodium bromide (≥98%, GPR RECTAPUR®; VWR cat. #: 27742.290)

- Copper (II) sulfate pentahydrate (≥98%, TECHNICAL; VWR cat. #: 23165.298)
- Silica Gel (NORMASIL 60® 40 - 63 µm; VWR cat. #: 27623.323)
- Hexane (≥98.5%, BAKER ANALYZED® ACS, J.T.Baker®; VWR cat. #: 9309-07)

Methods

Synthesis of Catalytic Complex: The primary catalyst, Cu(I)Br, was synthesized at the beginning of the experiment following a standard procedure. The catalytic complex was generated in a reaction flask by adding five equivalents (eq) of DMSO and 1 eq of piperidine to one eq of Cu(I)Br under vigorous stirring until a dark brown solution formed at room temperature during approximately 5 min.

Synthesis and Purification of Bioactive Compounds: The synthesis of terpene derivatives was conducted using a methodology developed in our laboratory based on atom transfer radical reactions. The catalytic complex described above was mixed with 10 eq of trichloroacetic acid derivative and 10 eq of the respective terpene. All reactions were performed for 90 minutes at 80°C. Reaction products were purified by column chromatography with NORMASIL Silica Gel using pure hexane as the solvent.

Characterization

- **Gas Chromatography-Mass Spectrometry (GC-MS):** An Agilent 8890 GC system with a 5977C MS spectrometer was used for reaction control and product characterization. Columns used DB-5ms 30m x 0.25mm, 0.25µm film,
- **Nuclear Magnetic Resonance (NMR):** NMR spectra were recorded on a Varian Mercury 300VX 300MHz spectrometer.

Microbiological Analyses of Cu(I) Catalytic Complexes: Microbiological tests were conducted using the disk-diffusion method [18, 19]. Fungal strains (*Aspergillus niger, Aspergillus ochraceus, Cladosporium linicola, Penicillium canescens*) were sourced from the YSU Research Institute of Biology's culture collection. The bacterial strain Xanthomonas vesicatoria 8846 was obtained from The National Culture Collection of Microbial Depository Center (MDC) of "Armbiotechnology" SPS NAS RA [20]. According to the bacteria's resistance profile, Azithromycin was used as a positive control for bactericidal effect [21]. Two positive controls were used: CuSO4 at the same concentration and the fungicidal preparation "Biopag-D," widely used for household disinfection [22-23].

Statistical Analyses: The statistical reliability of the experiments was assessed using standard methods [24-25]. All experiments were conducted in 5 series of 3 repeats each. Data analysis was performed using MS Excel, and the Standard Error of the Mean (SEM) was calculated to be ± 0.23–0.37. Significance was tested using the student t-test and considered significant at $p < 0.05$.

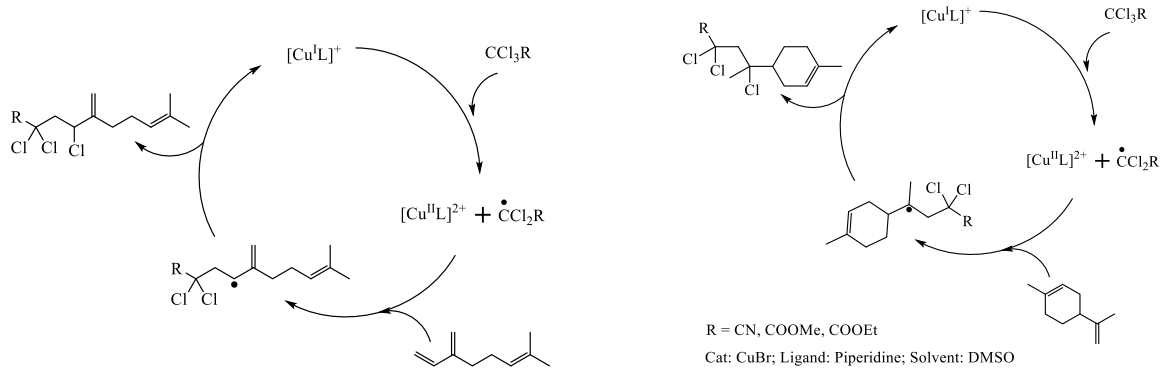
RESULTS

As previously noted, limonene and myrcene possess well-documented pharmacological properties, rendering them attractive candidates for functionalization to develop novel compounds with augmented physiological activities. The presence of reactive double bonds in these terpenes enables chemical modification, but concurrently increases the propensity for resinification, introducing complexities to the functionalization process.

In our laboratory, we have developed a novel methodology based on ATRR to functionalize these reactive terpenes efficiently. This method employs a highly active catalytic system of Cu(I)Br, further enhanced by the co-ligand solvent DMSO. The combination of Cu(I)Br and DMSO creates an excellent catalyst that facilitates the coupling of limonene and myrcene with various trichloroacetic acid derivatives, including trichloroacetonitrile, ethyl trichloroacetate, and methyl trichloroacetate.

The choice of Cu(I)Br as the catalyst in the ATRR methodology is based on its proven effectiveness in facilitating atom transfer processes through the homolytic cleavage of carbon-halogen bonds, thereby initiating radical formation. Cu(I) is particularly advantageous due to its ability to cycle between Cu(I) and Cu(II) states, which is essential for controlled radical reactions. In addition, DMSO was selected as the solvent due to its polar aprotic nature, which enhances the solubility of both Cu(I) and Cu(II) complexes, thereby promoting an efficient catalytic cycle. DMSO's role in stabilizing the active Cu complex and suppressing side reactions is crucial, as it leads to higher yields and better control over the polymerization process. Together, these factors contribute to the overall efficiency and selectivity of the ATTR reactions.

The developed methodology facilitates the synthesis of functionalized products with exceptional yields and purity, underscoring the versatility of ATRR in generating a broad spectrum of bioactive compounds. A comprehensive summary of reaction yields and product purities is provided in Table 1. The attained high yields and purities serve as a testament to the efficacy of our methodology, highlighting its potential for efficient and selective functionalization of limonene and myrcene.The lower yields observed with methyl and ethyl trichloroacetate compared to trichloroacetonitrile can be attributed to the reduced reactivity of ester groups in comparison to nitriles, which are more electrophilic and thus more reactive in ATRR. This effect is evident in lines 1 and 4, where trichloroacetonitrile provided significantly higher yields. Additionally, the higher yield of myrcene compared to limonene may be due to the higher reactivity of the conjugated diene system in myrcene, which is more prone to radical addition reactions than limonene's isolated double bond system. Furthermore, the extended reaction time and elevated temperatures required for the less reactive ester substrates likely promoted side reactions such as resignification, negatively affecting the final yield.



Scheme 1. Coupling of limonene and myrcene with trichloroacetic acid derivatives

Table 1. Yields and Purity of Functionalized Limonene and Myrcene Products

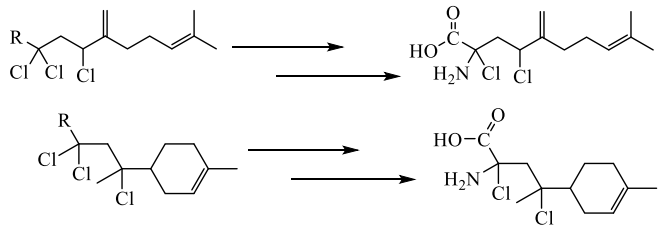
Line	Substrate 1	Substrate 2	Yield*	Purity*
1	Limonene	Trichloroacetonitrile	70	95%
2	Limonene	Methyl trichloroacetate	55	94%
3	Limonene	Ethyl trichloroacetate	53	94%
4	Myrcene	Trichloroacetonitrile	82	92%
5	Myrcene	Methyl trichloroacetate	62	91%
6	Myrcene	Ethyl trichloroacetate	65	95%

*Yield and purity have been calculated after purification

The functionalization through ATRR not only preserves the inherent bioactivity of these terpenes but also enhances their therapeutic potential by introducing new functional groups. Due to the insertion of carboxylic acid derivatives and chlorine into the molecular structure, these functionalized products exhibit high potential for further functionalization. Potential further pathways for these compounds include:

- Hydrolysis to the Acid State and Substitution of Chlorine:

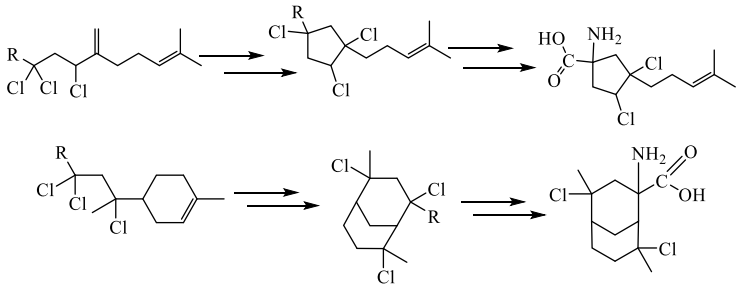
Theoretically, the hydrolysis of the carboxylic acid derivative and the subsequent substitution of chlorine in the alpha position could enable the synthesis of amino acid derivatives with a terpene tail.



Scheme 2: Potential Hydrolysis and Substitution to Amino Acid Derivative

Intramolecular Cyclization:

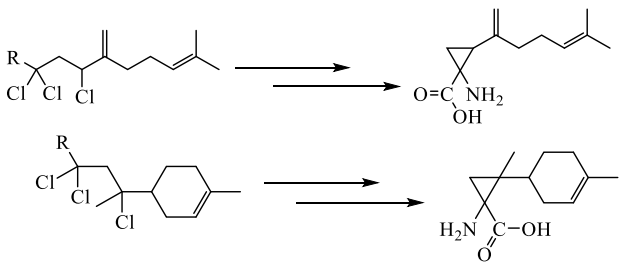
These compounds are assumed to undergo intramolecular cyclization via atom transfer radical cyclization (ATRC) reactions to yield functionalized carbocycles, which could then be transformed into amino acid derivatives.



Scheme 3: Proposed Intramolecular Cyclization to Functionalized Carbocycles

Dehalogenation to Cyclopropane Derivative:

Given the positioning of chlorine atoms in the 1-3 positions, it is hypothesized that dehalogenation can be performed to yield subsequent cyclopropane derivatives. These cyclopropane derivatives might also be functionalized to yield amino acid derivatives.



Scheme 4: Possible Dehalogenation to Cyclopropane Derivative

These additional pathways highlight the theoretical versatility and potential of the developed methodology for generating a wide array of bioactive compounds from limonene and myrcene. This innovative approach shows

potential for the development of novel therapeutic agents, contingent upon further biological investigation and validation. In addition to developing efficient synthesis methodologies, the principles of green chemistry emphasize the importance of waste minimization and environmentally benign processes. In this context, we investigated the potential use of wastewater from Cu(I) catalytic systems for their antibacterial and antifungal activities. This approach not only aligns with green chemistry principles but also explores the dualistic nature of Cu ions, which can act as both growth activators and inhibitors depending on concentration [26].

The *in vitro* study of the Cu(I) catalytic system demonstrated bactericidal and fungicidal activity against some pathogenic fungi and phytopathogenic bacteria. At a 3% concentration, the solutions exhibited significant inhibitory effects, while at 0.03%, they showed growth promotion.

Table 2: Bactericidal Activity against *Xanthomonas vesicatoria 8846* Phytopathogen.

Sample	**Biological Effect (in mm) on *Xanthomonas vesicatoria 8846***	
	1-st petri dish	**2-nd petri dish**
3 % CuSO4	**–**	17 mm zone of growth inhibition
1 % CuSO4	**–**	14 mm zone of growth inhibition
0.03 % CuSO4	Dualistic influence: 15 mm zone of growth stimulation, inside of which we have 5 mm zone of secondary growth inside of zone of inhibition. The transparent halo is visible in the middle of observed rounds of growth zones. It is the zone of the growth inhibition (2 mm width)	15 mm zone of growth stimulation
0.03 % [Cu]x	15 mm zone of growth stimulation	**–**

Table 3: Fungicidal Activity against *Aspergillus niger* and *Penicillium canescen.*

Preparation	**Diameter of zone of inhibition**	
	Aspergillus niger	***Penicillium canescens***
"Biopag" (positive control N 1)	**25**	**15**
(Positive control N 2) $CuSO_4$ pH=4,8 C_{Cu}=3 g/kg	**9**	**6,35**
Cu (I) catalytic complex pH=4,8 C_{Cu}=3 g/kg	**0**	**0**

These results suggest that the compounds could be used as growth activators or inhibitors, depending on the concentration, thereby offering potential applications in agriculture and biotechnology (Fig. 1 – 2).

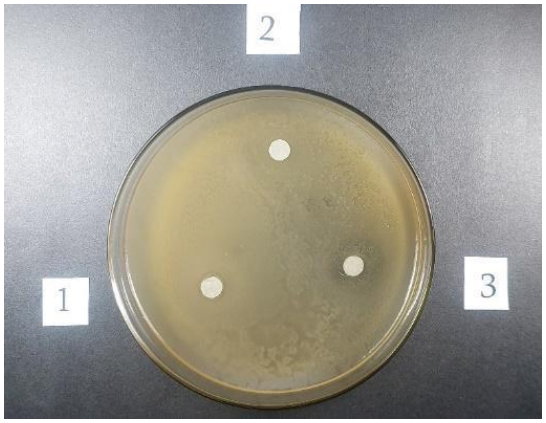


Fig. 1. Bactericide activity in 0.03% (1), 1% (2) и 3% (3) concentrations against *Xanthomonas vesicatoria 8846* strain.

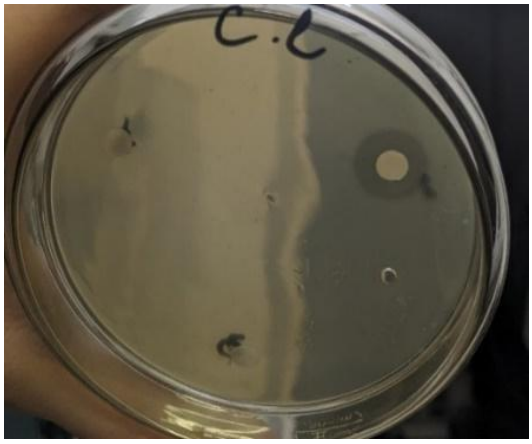


Fig. 2. Fungicide activity against *Cladosporium linicola* in 3% concentration.

According to the literature data the influence of Cu ions can have a dualistic effect on various types of cells, which is potentially usable for modulating cell growth [27, 28]. Different forms of Cu can have both growth activator and inhibitory influence on fungi [29, 30]. These findings are consistent with literature data suggesting that the influence of Cu ions can have a dualistic effect on various types of cells, which is potentially useful for cell growth modulation. Different forms of Cu can act as both growth activators and inhibitors for fungi, making them versatile agents in biological applications [31].

DISCUSSION

The results of our study demonstrate the effectiveness of ATRR for the functionalization of limonene and myrcene, achieving high yields and purities [32,33]. This success underscores the potential of ATRR methodologies in synthesizing bioactive compounds from natural terpenes, aligning with the principles of green chemistry by utilizing renewable resources and minimizing waste.

1. Efficiency and Yield: The high yields and purities obtained (Table 1) indicate that ATRR is a robust and efficient method for functionalizing limonene and myrcene. The catalytic system, comprising Cu(I)Br and DMSO, proved highly effective, facilitating the coupling with various trichloroacetic acid derivatives. This efficiency is crucial for the sustainable production of bioactive compounds, reducing the need for extensive purification processes and thereby minimizing chemical waste.

2. Therapeutic Potential: The functionalization of terpenes through ATRR preserves their inherent bioactivity and enhances their therapeutic potential. By introducing new functional groups, the synthesized compounds exhibit properties that could lead to the

development of new pharmaceuticals [34-36]. These transformations enhance the versatility of the synthesized compounds, paving the way for the creation of amino acid derivatives and functionalized carbocycles [37].

3. Green Chemistry Principles: Our methodology aligns with the principles of green chemistry, emphasizing waste minimization and the use of environmentally benign processes. Terpenes as starting materials leverage their natural abundance and bioactivity, offering a sustainable alternative to traditional chemical feedstocks [38]. Furthermore, the dualistic nature of the Cu(I) catalytic system, exhibiting both bactericidal and fungicidal activities, demonstrates the potential for reutilizing wastewater, thereby contributing to a circular economy [39].

4. Antibacterial and Antifungal Activities: Cu has a dualistic influence on living organisms. Several low concentrations are necessary for the regular metabolic activity of Cu-dependent enzymes (oxidoreductases, etc.). These enzymes, like nitrogen oxide reduction, are responsible for oxygenation and oxidation [40]. *In vitro* studies of the Cu(I) catalytic system exhibited significant bactericidal and fungicidal activities at a 3% concentration, with notable inhibitory effects on pathogenic fungi and phytopathogenic bacteria. Interestingly, at a 0.03% concentration, the catalytic system showed growth-stimulating activity. These findings are consistent with literature data, highlighting the dualistic effect of Cu ions on cell growth modulation. The potential applications of these findings in agriculture and biotechnology are noteworthy, suggesting that the catalytic system could serve as both growth activators and inhibitors, depending on the required concentration [41].

5. Future Directions: The promising results obtained in this study pave the way for further research. Future studies should focus on the detailed biological evaluation of the synthesized compounds to validate their therapeutic potential [42]. Additionally, exploring the environmental impact of ATRR and the reutilization of catalytic wastewater in agricultural applications could further solidify the methodology's alignment with green chemistry principles.

CONCLUSION

This study introduces a sustainable and efficient ATRR methodology for functionalizing limonene and myrcene, achieving high yields and purities. Uniquely, this research demonstrates the dualistic antibacterial and antifungal activities of the Cu(I) catalytic system, which enhances therapeutic potential and offers novel applications in agriculture and biotechnology. Utilizing renewable resources and minimizing waste, aligns with green chemistry principles, contributing to both medicinal chemistry and sustainable agriculture. Future work should further validate these findings and explore the broader environmental impact of ATRR.

Abbreviations: ATRA, Atom Transfer Radical addition; ATRC, Atom Transfer Radical Cyclization; DMSO, dimethyl sulfoxide; SEM, Standard Error of the Mean; GC-MS, Gas Chromatography-Mass Spectrometry; NMR, Nuclear Magnetic Resonance.

Author's Contributions: All authors contributed to this study.

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