ORIGINAL ARTICLE

A C G publications

Rec. Nat. Prod. 15:6 (2021) 593-601

records of natural products

Microbial Transformation of (–)-α-Bisabolol Towards Bioactive Metabolites

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(Received April 15, 2020; Revised April 06, 2021; Accepted April 10, 2021)

Abstract: Bisabolol is one of the bioactive constituents of chamomile. It was aimed to biotransform (–)-*α*-bisabolol by different fungi for the production of new bioactive metabolites, which was converted to *α*-bisabolol oxide A and B by *Thamnidium elegans*. Additionally, the biotransformation by *Penicillium neocrassum* yielded a new metabolite, which was characterized as 2-(5-methyl-5-(6-methyl-7-oxabicyclo[4.1.0]heptan-3-yl)tetrahydrofuran-2-yl)propan-2-ol = bisafuranol. The substrate and its metabolite mixtures were tested using antioxidant DPPH$^{\bullet}$ scavenging assay. Antimicrobial activity was evaluated by an *in vitro* microdilution assay against a panel of human pathogenic bacteria and yeasts resulting in the lowest MIC and MFC values of 150 µg/mL. (–)-*α*-Bisabolol was effective against *Propionibacterium acnes* and *Staphylococcus epidermidis* (75, 37.5 µg/mL, respectively). The antioxidant activity of the metabolites was found to be more effective in scavenging free radicals.

Keywords: *Matricaria recutita* L.; microbial transformation; bisabolol; antimicrobial activity; antioxidant activity; *Penicillium neocrassum*.

1. Introduction

Terpenes constitute one of the largest chemical classes of secondary metabolites. Terpenes and terpenoids with low molecular weights such as mono- and sesquiterpenes are also characteristic volatile constituents of essential oils [1]. Terpenes withdraw attention due to their broad biological activities in many sectors [2]. Biotechnological applications such as biotransformations of terpenes and terpenoids have an important impact for food, chemicals and pharmaceuticals [3–5].

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The article was published by ACG Publications
http://www.acgpubs.org/journal/records-of-natural-products November-December 2021 EISSN:1307-6167
DOI: http://doi.org/10.25135/rnp.252.2004.1615

(–)-α-Bisabolol also known as levomenol, is a natural monocyclic sesquiterpene alcohol, which is mainly found in chamomile - *Matricaria recutita* L. (Asteraceae) essential oil [6]. The oxidation products of bisabolol are bisabolol oxide A and B. There are two types of chamomile essential oils, which are characterized and defined namely as "bisabolol oxide type", or "α-bisabolol type" [7]. (–)-α-Bisabolol rich essential oils and their preparations are used mainly in the traditional medicines as well as in cosmetics, fragrances and pharmaceuticals [7,8]. Bisabolol is known to possess antioxidant [9], anti-irritant, anti-inflammatory [10], and anti-microbial properties [11], among others.

Natural compounds, which are difficult to synthetize can be derivatized biotechnologically by microbial transformations for the production of flavor or fragrance substances or other technical applications [12]. According to the literature, the biotransformation of monoterpenes was studied quite extensively over the past 40 years [13–15], however the biotransformation of sesquiterpenes such as α-bisabolol is still a challenge. As retrieved by current literature search, Miyazawa and co-workers reported the transformation of (–)-α-bisabolol by *Glomerella cingulata*, yielding the oxygenated products defined as (1*S*,3*R*,4*R*,7*S*)-3,4-dihydroxy-α-bisabolol, and bisabolol oxide B. In addition, (1*S*,3*R*,4*R*,7*S*)-3,4-dihydroxy-α-bisabolol was further transformed to (1*S*,3*R*,4*R*,7*S*,10*S*)-3,4-dihydroxy-bisabolol oxide B, where bisabolol oxide B was derivatized to (1*S*,3*R*,4*R*,7*S*,10*S*)- and (1*S*,3*S*,4*S*,7*S*,10*S*)-3,4-dihydroxy-bisabolol oxide B [16]. Other scientific reports on (–)-α-bisabolol biotransformation by *Aspergillus niger* resulted in (-)-α-bisabolol oxide B [17], (–)-α-tetrahydrobisabolen-2,5,6-triol [18], and 6-methyl-2-(4'-methylcyclohexan-1'-yl)-2,5-epoxyheptane-3',4',6-triol [19]; whereas the biotransformation by *G. cingulata* resulted in the formation of the metabolites (2*S*,5*S*,1'*S*,3'*R*,4'*R*)-6-methyl-2-(4'-methylcyclohexane-1'-yl)-2,5-epoxy-heptane-3',4',6-triol [20], and (2*S*,5*S*,1′*S*,3′*S*,4′*S*)-6-methyl-2-(4′-methylcyclohexane-1′-yl)-2,5-epoxy-heptane-3′,4′,6-triol [21], respectively. In addition, *Bipolaris sorokiniana* was used for the biotransformation of α-bisabolol by oxidative conversion to bisabolol oxide B as exogenous substrate [22], which was one of the last publications on the topic.

The main aim of this present study was to evaluate the biotransformation of (–)-α-bisabolol by different microorganisms to yield new bioactive metabolites, and ways for natural product derivatisation. Thus, (–)-α-bisabolol was biotransformed by *Thamnidium elegans, Mucor ramannianus, Trichoderma harzianum* and *Penicillium neocrassum* among other tested microorganisms. Not only biotransformation studies, but also *in vitro* biological activity studies were performed both on the substrate and its metabolites subsequently, which is reported for the first time to the best of our knowledge.

2. Materials and Methods

2.1. Substrate and Chemicals

The substrate (–)-α-bisabolol (> 93%) was purchased from Sigma-Aldrich, which was used for biotransformation and bioactivity studies. All other chemicals used were in analytical grade and were acquired by Sigma-Aldrich, Fluka or Merck unless otherwise stated.

2.2. Microbial Strains

Bacterial, fungal and yeast strains/isolates used in the present study were obtained from the US Agricultural Research Service Culture Collection (NRRL), American Type Culture Collection (ATCC), and were deposited at the Department of Pharmacognosy, Faculty of Pharmacy, Anadolu University, Eskisehir, Turkey.

2.3. Cultivation of Fungi and Microbial Transformation

(–)-α-Bisabolol (50 mg) was biotransformed using *Thamnidium elegans* ATCC 18191, *Mucor ramannianus* ATCC 1839, *Trichoderma harzianum* (isolate T, Faculty of Sciences, Anadolu University), and *Penicillium neocrassum* NRRL 35639. To refresh the microbial cultures, Sabouraud glucose agar (SGA, Fluka) was used initially and purity check was performed. At the same time a

liquid broth (*α*-medium) which consisted of glucose 20 g, peptone 5 g, yeast extract 5 g, NaCl 5 g, and Na_2HPO_4 5 g per Liter was prepared. 250 mL sized Erlenmeyer flasks containing autoclaved 100 mL *α*-medium were inoculation at 27 °C for two days at 150 rpm using a shaking incubator. Biotransformations were carried out by adding the substrate (–)-*α*-bisabolol (50 mg/flask, dissolved in 500 μL acetone) under aseptic conditions, which was cultivated for 14 days.

2.4. Extraction of Biotransformation Metabolites

After incubation, the mycelium was removed by filtration, and the broth was extracted successively with EtOAc (min. 3 x 100 mL). The resulting extract was dried over anhydrous sodium sulphate (Na_2SO_4) and evaporated under vacuum. The same procedures were applied for the biotransformation controls; *α*-medium, medium without substrate, and medium without microorganisms. Biotransformation extracts were obtained for *T. elegans* (**E1**), *M. ramannianus* (**E2**), *T. harzianum* (**E3**) and *P. neocrassum* (**E4**), respectively.

The substrate (–)-*α*-bisabolol (**B**) and the metabolite mixtures produced by *T. elegans* (**E1**), *M. ramannianus* (**E2**), *T. harzianum* (**E3**), and *P. neocrassum* (**E4**) were analyzed by TLC, GC and GC-MS and were evaluated for *in vitro* antioxidant and antimicrobial activities.

2.5. Analytical and Preparative Thin Layer Chromatography (TLC, prep. TLC)

All samples were analyzed by TLC to confirm the presence of biotransformed metabolites. TLC analyses were performed on silica gel 60 GF_{254} (Merck) using chloroform-toluene (3 : 1, v/v) as mobile phase. Followed by UV visualization; or/ and anisaldehyde/sulphuric acid + heating at 110 °C for the visualization of substrate and metabolites. Metabolite **M8** was purified by using successive prep. TLC from the extract.

The major metabolite **M8** (94% by GC-FID) biotransformed by *P. neocrassum* was purified on prep. TLC and further evaluated by chromatographic and spectroscopic techniques.

2.6. Gas Chromatography and Gas Chromatography-Mass Spectrometry (GC, GC-MS)

The biotransformed metabolites were identified by GC (Agilent 6890N GC system) and GC-MS (Agilent 5975 GC-MSD system) analyses (supporting information Materials and Methods S1 for details). As shown in supporting information Table S1, the formation of metabolites was observed, which were defined as **M1**, **M2**, **M3**, and **M4** by *T. elegans;* **M5** and **M6** by *M. ramannianus;* **M7** by *T. harzianum;* and **M8** by *P. neocrassum***,** respectively.

*α-Bisabolol oxide B (**M1**)*: EI-MS (70 eV): *m/z* (%) 238 (2) $[M]^+$, 220 (5), 205 (3), 179 (27), 161 (55), 143 (100), 134 (39), 125 (34), 107 (24), 105 (74), 95 (27), 85 (58), 71 (35), 59 (47), 43 (55) data was in accordance with Miyazawa et al. [16].

*α-Bisabolol oxide A (**M2**)*: EI-MS (70 eV): *m/z* (%) 238 (1) $[M]^+$, 220 (2), 180 (3), 159 (3), 143 (100), 134 (18), 125 (36), 107 (26), 93 (37), 81 (12), 71 (24), 59 (17), 43 (40) data was in accordance with Hashidoko et al. [23].

2.7. Spectroscopic and Physical Analysis

1D- (^{1}H- and ^{13}C-NMR) and 2D- (COSY, HSQC and HMBC) experiments were performed. The NMR analysis was carried out at Anadolu University-BIBAM Research Centre, Eskisehir (Turkey). 1D- and 2D-NMR spectra were recorded on a Bruker 500 MHz FT-NMR spectrometer in $CDCl_3$. FT-IR spectroscopy were performed on KBr pellets by means of Perkin Elmer Spectrum (100 Model, USA). High resolution mass spectra analysis was done with a LC-MS-IT-TOF (Shimadzu Corporation, Kyoto, Japan). Optical rotation was measured on a polarimeter (Krüss Optronic P8000-T, Germany).

*2-(5-methyl-5-(6-methyl-7-oxabicyclo[4.1.0]heptan-3-yl)tetrahydrofuran-2-yl)propan-2-ol (bisafuranol, **M8**)*: A pale yellow oily compound visualized by anisaldehyde/sulphuric acid derivatisation color: yellow; $[a]_D^{25}$ = -6.6 (*c* 0.01, EtOAc); HR-MS [ESI-TOF]: *m/z* $[M + Na]^+$ calcd. for $C_{15}H_{26}O_3Na$: 277.1774; found: 277.1753. FT-IR (KBr): 3710, 2925, 1455, 1379, 1261, 1081,1021 cm^{-1}, EI-MS (70 eV): *m/z* (%) 239 (1) $[M^+-CH_3]$, 221(3), 195(2), 177(26), 159(25), 149(43), 143(100), 133(22), 125(32), 119(12), 107(32), 93(31), 85(35), 71(30), 59(32), 43(72); ^{1}H-NMR (in $CDCl_3$, 500 MHz), ^{13}C-NMR (in $CDCl_3$, 125 MHz) details are listed in Table 2.

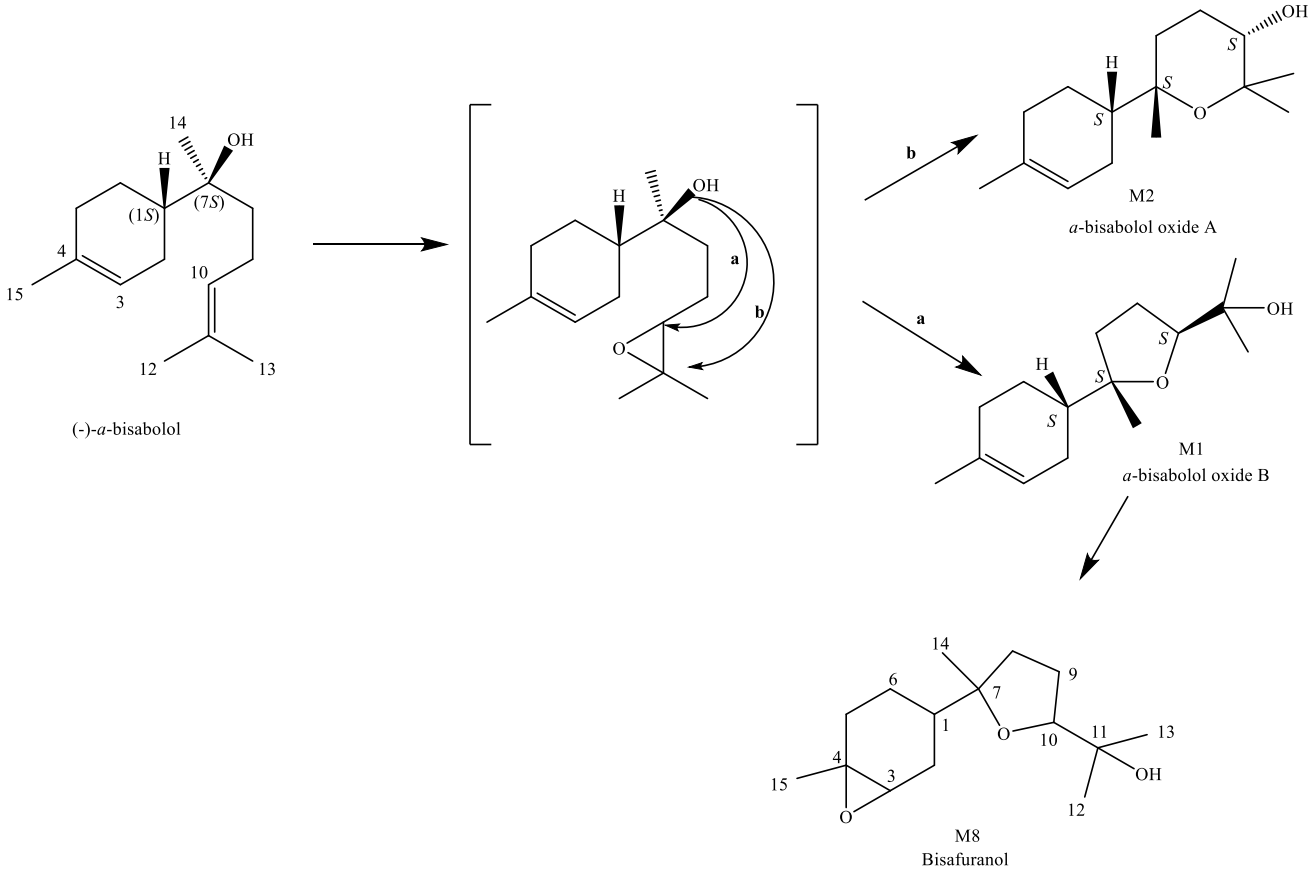

Figure 1. Metabolic pathway of (–)-α-bisabolol by *T. elegans* and *P. neocrassum* [16, 24].

2.8. In vitro Antimicrobial Activity

A microdilution broth susceptibility assay was used, as previously described [25,26]. The bacterial strains used were *Escherichia coli ATCC* 8739, *Propionibacterium acnes* ATCC 6919, *Staphylococcus epidermidis* ATCC 12228, *Salmonella typhimurium* ATCC 13311 and *Staphylococcus aureus* ATCC 6538. The yeast used were *Candida albicans* ATCC 10231 *and C. glabrata* (clinical isolate, Eskisehir Osmangazi University, Faculty of Medicine) and *C. utilis* NRRL Y-900, respectively.

Minimum bactericidal or fungicidal concentration (MIC/MFC) values of (–)-α-bisabolol and biotransformation extracts (**E1-4**) were evaluated by broth microdilution method using u-shaped 96-well microtiter plates (Sigma, Germany). Amoxicillin and chloramphenicol were used as standard antibacterial agents, whereas amphotericin B and nystatin were used as standard antifungal agents at a concentration range of 0.125-32 μg/mL. All tests were assayed in duplicate in two independent experiments and MICs/MFCs were reported as mean (Please see supporting information Materials and Methods S2 for details).

2.9. Free Radical Scavenging Activity

The 1,1-diphenyl-2-picrylhydrazyl• (DPPH•) scavenging activity was determined according to the previous report of Kumarasamy et al. [27]; DPPH• (8 mg) was dissolved in MeOH (100 mL). (–)-*α*-Bisabolol and the biotransformation extracts were dissolved in DMSO at the concentration of 1 mg/mL. Ascorbic acid was used as reference standard at the same concentration. The stock solutions were serially diluted using a 96 well plate. Test samples and standard solution (100 µL each) were reacted with equal amount of DPPH• solution, for 30 min at room temperature. The resulting absorbance was measured at 517 nm using a microplate reader. Radical scavenging capacity was expressed as percentage inhibition (I%) and calculated using the following equation:

$$(I\%) = [(Abs_{control} - Abs_{sample})/Abs_{control}] \times 100$$

3. Results and Discussion

3.1. Microbial Transformation and Analysis of Metabolites

After initial screening using different microorganism, successful biotransformation experiments were focused on *T. elegans*, *M. ramannianus*, *T. harzianum, P. neocrassum,* respectively.

According to the GC-FID and GC-MS analyses, totally eight metabolites namely; *α*-bisabolol oxide B (**M1**), *α*-bisabolol oxide A (**M2**), and unidentified metabolites (**M3**, **M4**, **M5**, **M6**, **M7**) were detected and partially characterized in the biotransformation broth extracts.

According to the biotransformation results of (–)-*α*-bisabolol using *T. elegans; α*-bisabolol oxide B (**M1**, 10%) and *α*-bisabolol oxide A (**M2**, 20%) and unidentified metabolites (**M3**, 7% and **M4**, 10%) were produced (for supporting information see Table S1). The identification of the separated metabolite mixture **E1** was through the comparison of MS data and retention time (RT) of standards compared with the in-house mass libraries.

As shown in Figure 1, biotransformation metabolites (**M1** and **M2**) were determined by GC-MS analysis from the metabolite mixture **E1**. The EI-MS of **M1** and **M2** showed a molecular ion at *m/z* 238, corresponding to the molecular formula of $C_{15}H_{26}O_2$. Oxidation of (–)-*α*-bisabolol produced the **M1** and **M2** metabolites, which were identified as *α*-bisabolol oxide B and *α*-bisabolol oxide A, respectively.

It is well known that microorganisms such as fungi are capable to perform oxidation, reduction, isomerization reactions enzymatically, among other specific reactions. According to previous reports, *Thamnidium elegans* is used in biotransformations due to its allylic hydroxylase activity [28]. Also, it is known that bisabolol oxides may be vulnerable to allylic hydroxylation [29].

*3.2. Biotransformation of (–)-α-Bisabolol by P. neocrassum (**E4**)*

Metabolite **M8** was purified by prep. TLC eluting with chloroform-toluene (3:1) to isolate a pale-yellow oily compound. With the aid of GC-FID, GC-MS, NMR and FT-IR, the new metabolite **M8** was hypothesized to be a "bisabolol oxide B type derivative", comprising the molecular formula $C_{15}H_{26}O_3$. The molecular ion peak at *m/z* 254, showed a methyl loss as observed at the 239 $[M^+-CH_3]$ ion, and *m/z* 143, as the base peak. The epoxide intermediate of **M8** was formed by the nucleophilic attack of 7-OH on the 10,11-double bond, and the tetrahydrofuran ring was formed upon epoxidation of *α*-bisabolol, and was observed from the base peak at *m/z* 143, which was confirmed also by literature [23]. Meanwhile, the metabolic route leading to cyclohexene epoxide occurred by the C-3, C-4 double bond attack as biotransformed by *P. neocrassum,* which is shown in Figure 1. The molecular formula $C_{15}H_{26}O_3$, with two degrees of unsaturation was deduced by the HR-MS, pseudomolecular ion peak at m/z 277.1753 ($[M+Na]^+$), and inspection of the NMR data (Table 2), respectively. The ^{1}H-NMR spectrum contained signals for four tertiary methyl groups at δ_H 1.31, 1.20, 1.12, and 1.08; and two isolated oxymethine resonances at δ_H 3.76 (t, 7.2 Hz), and 2.99 (brd, 5.4 Hz), respectively. The ^{13}C NMR spectrum displayed 15 carbon signals, which are four methyl, five methylene, three methine and three quaternary carbons. The presence of a tetrahydrofuran ring was

evident from the signals at δ_H 3.76 (t, J = 7.2 Hz), and two non-equivalent CH_2 signals at δ_H 1.75 (m)/1.50 (m) and 1.85 (m)/1.72 (m). The other unsaturation was arising from a tri-substituted cyclohexane moiety, which was inferred from the signals at δ_H 2.99 (brd, J= 5.4 Hz), δ_H 1.58 (m) and three CH_2 signals at δ_H 1.99 (m), 1.52 (m)/1.20, and 2.04 (m)/1.63 were observed in the same spin system in the COSY spectrum. The carbon signals at 59.2 and 57.7 were characteristic for an epoxy function on the cyclohexane moiety. The positions of the methyl groups as well the connections of the two cycles to each other were established using the HMBC spectrum (Table 2). The long-range correlation between C-3 and Me-15, as well as between C-4 and Me-15 indicated that the attachment site of Me-15 should be C-4. Similarly, the long-range coupling of C-10 with Me-12 and Me-13 led to the connection of both methyl groups at C-11. The other key cross-peak was evident between C-1 and Me-14 indicating the location of Me-14 to be C-7, and the connection of the cycles as drawn in Figure 1. The absolute configurations at C-1, C-3, C-4, C-7 and C-10 could not be established, due to low amounts remained, which resulted in poor quality NMR data. However, the angle and distance between the H atoms at position 3, and the 2 H atoms at the 2 position, confirmed the epoxidation stereochemistry according to the MOPAC analyses as shown in Figure S22, within the supplementary data. The IR-spectrum showed a broad absorption at 3710 cm^{-1} for O-H, at 2925 cm^{-1} for C-H stretching, 1455 and 1379 cm^{-1} for C-H bending of methyl groups, at 1261, 1081 and 1021 cm^{-1} for C-O, respectively. To be best of our knowledge, metabolite **M8** is characterized, and reported for the first time and named as 2-(5-methyl-5-(6-methyl-7-oxabicyclo[4.1.0]heptan-3-yl)tetrahydrofuran-2-yl)propan-2-ol according to IUPAC nomenclature (acronym: **bisafuranol**) in this present study, as shown in the supplementary file Figure S14. To avoid confusion, the authors used the classical terpene numbering system in accordance with literature [16-21 and references cited herein] throughout the manuscript.

Table 2. ^{13}C and ^{1}H NMR data and key HMBC for metabolite **M8**

Position	δ_C(ppm)	δ_H(ppm), J (Hz)	HMBC (C→H)
1	43.0	1.58 m	H_2-2, H-3, H_3-14
2	26.3	1.99 m	
3	59.2	2.99 brd (5.4)	H-1, H_3-15
4	57.7	-	
5	30.8	2.04 m	H_3-15
		1.63 m	
6	20.5	1.52 m	
		1.20 m	
7	84.8	-	H_3-14
8	34.8	1.75 m	H_3-14
		1.50 m	
9	26.2	1.85 m	
		1.72 m	
10	83.8	3.76 t (7.2)	H_3-12, H_3-13
11	71.4	-	H_2-9, H_3-12, H_3-13
12	24.2	1.12 s	
13	27.2	1.20 s	
14	21.8	1.08 s	
15	22.9	1.31 s	

Abbreviations: Assignments are based on COSY, HSQC and HMBC experiments. s; singlet, d; doublet, t; triplet, m; multiplet, br; broad.

Bisabolol oxides A and B possess a very distinctive fragmentation pattern, with a base peak at *m*/*z* 143 and secondary fragmentation peaks at *m*/*z* 125, 107, and 71. The metabolites **M4**, **M5**, **M6**, **M7**, and **M8** having a similar structure to bisabolol oxides A and B exhibited similar fragment ions with a base peak at *m*/*z* 143, as well as additional fragmentation peaks at *m*/*z* 125, 107, and 71, respectively [29]. The MS spectra of the metabolites were similar to bisabolol oxides, suggesting a close structural relationship (supporting information Table S1).

Except metabolite **M8**, other metabolites could not be separated in high purity, which is still under progress. In addition, the metabolite **M3** (base peak at *m/z* 94) could also not be characterized, thus only MS data was provided as reported in supporting information Table S1.

3.3. In vitro Antimicrobial Activity

The antibacterial and antifungal activity results of (–)-*α*-bisabolol compared with the metabolite mixtures (**E1**, **E2**, **E3**, **E4**) and standards are given in Tables 3 and 4 observed as MIC and MFC values, respectively. As shown in Table 3 and Table 4, antimicrobial activity test results showed no substantial activity when compared with the antibacterial standards amoxicillin, chloramphenicol, and the antifungal standards amphotericin B and nystatin, respectively.

Table 3. Antibacterial activity of (–)-*α*-bisabolol and metabolite mixtures (MIC, μg/mL)

Bacterial strains	**B**	**E1**	**E2**	**E3**	**E4**	**AMX**	**CAM**
E. coli	>300	>300	>300	>300	>300	8	4
P. acnes	75	>300	>300	>300	>300	≤0,125	2
S. epidermidis	37,5	>300	>300	150	>300	≤0,125	2
S. typhimurium	300	>300	>300	>300	>300	0,250	8
S. aureus	300	>300	150	>300	>300	1	4

Abbreviations: B, (–)-*α*-bisabolol; biotransformation mixture by *T. elegans,* E1; *M. ramannianus,* E2; *T. harzianum,* E3*;P. neocrassum,* E4; AMX, amoxicillin; CAM, chloramphenicol

Table 4. Antifungal activity of (–)-*α*-bisabolol and metabolite mixtures (MFC, μg/mL)

***Candida* strains**	**B**	**E1**	**E2**	**E3**	**E4**	**AMPB**	**NY**
C. albicans	>300	>300	>300	>300	>300	32	4
C. glabrata	>300	>300	>300	>300	>300	16	2
C. utilis	300	300	300	150	300	2	1

Abbreviations: B, (–)-*α*-bisabolol; biotransformation mixture by *T. elegans,* E1; *M. ramannianus,* E2; *T. harzianum,* E3*;P. neocrassum,* E4; AMPB, amphotericin B; NY, nystatin

Bisabolol and chamomile oils are regarded as generally safe as, which are used in a wide range of cosmetic formulations such as a skin conditioning agent among others [6]. *P. acnes* and *S. epidermidis* are opportunistic pathogens associated with skin diseases such as acne. Therefore, in the present study, we evaluated the antibacterial activity of (–)-*α*-bisabolol and its biotransformed products in the same fashion. (–)-*α*-Bisabolol exhibited more activity against *P. acnes, S. epidermidis* (MIC 75 μg/mL and 37,5 μg/mL respectively), whereas (–)-*α*-bisabolol a weak activity towards *S. typhimurium* and *S. aureus* (MIC 300 μg/mL). Although all metabolite mixtures exhibited poor antibacterial activity against *E. coli*, *P. acnes, S. typhimurium* (MIC > 300 μg/mL); metabolite mixtures produced by *M. ramannianus* (**E2**) showed relatively more growth inhibitory activities against *S. aureus* (MIC 150 μg/mL)*;* whereas metabolite mixtures produced by *T. harzianum* (**E3**) inhibited *S. epidermidis* (MIC 150 μg/mL).

(–)-*α*-Bisabolol and **E1-4** metabolite mixtures appeared as inactive against *C. albicans* and *C. glabrata* (MFC > 300 μg/mL). **E3** metabolite mixture showed a moderate activity towards *C. utilis* (MIC 150 μg/mL), whereas (–)-*α*-bisabolol and other metabolite mixtures (**E1**, **E2**, **E4**) a weak activity towards *C. utilis* (MFC 300 μg/mL).

3.4. In vitro Antioxidant Activity

Ascorbic acid as a positive control exhibited high antioxidant activity with 92.05% at 1 mg/mL. Experimental *in vitro* antioxidant results showed that metabolite mixtures are relatively more active (**E1**= 31.3%, **E2**= 28.5%, **E3**= 32.0%, **E4**= 32%, respectively) compared to (–)-*α*-bisabolol with 6.25% inhibition at the same concentrations (as shown in the supporting information on Figure S23). Although bisabolol was claimed as a remarkable antioxidant, experimental results suggested that it is relatively weak in scavenging DPPH radicals (> 449.7 μM) [30].

Although a limited number of microbial transformation studies are available in the literature, especially on bisabolol and its derivatives, new insights into the biological activity of their metabolites are limited. In this present study, it was shown that several new metabolites were formed. For the first time that the new compound was 2-(5-methyl-5-(6-methyl-7-oxabicyclo[4.1.0]heptan-3-yl)tetrahydrofuran-2-yl)propan-2-ol, which was named: bisafuranol. Biotransformations as a biotechnological derivatization tool have still a high impact in producing bioactive compounds.

Acknowledgments

This work was supported by the Anadolu University Scientific Research Projects (BAP-1401S008) fund, which is part of the PhD thesis of ZF and was partially presented at the European Biotechnology Congress 2017, 25-27 May, Dubrovnik, Croatia and J. Biotech. 256, suppl. 30, S52-S53 (2017). The authors would like to thank AUBIBAM for spectroscopic analyses also to Dr. Serkan Levent, Prof. Dr. İlhami Çelik, Doç. Dr. Özer Gök, Prof.Dr. Atilla Akdemir and the RNP editorial for analytical support.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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