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USA-Kenya Collaboration in Natural Products Research Involving Isolation of Medicinal Compounds from Zanthoxylum Usambarense

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Abstract

The present research is part of an ongoing USA-Kenya collaboration in medicinal chemistry. The overarching goal is to enhance multicultural and professional development opportunities for faculty members, undergraduates, and graduate students. We unanimously chose a common topic involving medicinal plants endemic to Kenya. The use of medicinal plants dates back to the 15th century when hundreds of plants were used in traditional medicine. To date, medicinal plants are still used in some developing countries primarily because they are readily available and cheaper than pharmaceutical drugs. The earliest historical records of herbs are found from the Sumerian civilization, where different medicinal plants including opium were used. In Kenya, *Zanthoxylum usambarense* (Engl.) Kokwaro is used in herbal medicine to treat different diseases. The present study is aimed at assessing the antimicrobial activity of extracts from *Z. usambarense* plant materials that were collected from Elgeyo Marakwet County, Kenya. The plant materials were taken to the chemistry laboratory at the University of Kabianga. Crude extracts and pure compounds were isolated from the plant materials and biotested for antimicrobial activity. *Staphylococcus aureus* was used as the biological test organism. Undergraduate and graduate students played an integral part in implementing the research project. The bioassay data provided lead compounds that could be further developed as natural antibiotics for the treatment of bacterial and fungal infections.

Keywords: Natural products; *Zanthoxylum usambarense*; Antimicrobial activity; Structural elucidation; Nuclear magnetic resonance (NMR) spectroscopy; Mass spectrometry; Mentoring undergraduate and graduate students

Introduction

Zanthoxylum usambarense (Engl.) Kokwaro [1,2] also known as Fagara usambarensis (Engl. 1905), Fagara becquetii and Zanthoxylum becquetii, belong to the family Rutaceae [3]. It is a much-branched tree up to 15 meters tall with conical woody protuberances 2-3cm long ending in sharp straight thorns 5-9mm long. It has a bark rough with longitudinal ridges and furrows as deep as 5 m, greyish brown, peeling yellow underneath and branches with sharp straight to slightly up curved dark red prickles 6-12mm long [1]. Leaves are usually alternating, and flowers are unisexual. The fruits are usually a pair of almost globose follicles.

Z. usambarense is highly valued as an important medicinal plant. It is found in Ethiopia, Kenya, Tanzania, and Rwanda [1]. In Ethiopia, a dried stem infusion is taken as a remedy for kidney infections while fresh stem bark is crushed and used to poultice swollen joints [4]. A stem bark and root bark decoction are commonly taken by the Maasai people of Kenya as an emetic and purgative as well as for the treatment of malaria, backache, joint pain, and rheumatism. The fruits and the leaves are chewed to treat mouth infections, intestinal worms, diarrhea, dysentery, cough, vomiting, and stomachache. An infusion of the fruit is mixed with milk to treat fever, sore throat, tonsillitis, and chest pains. A hot decoction of the seeds is taken to treat malignant catarrhal fever and respiratory tract infections.

In Kenya, *Z. usambarense* plant is used for dying clothes. The root and stem barks yield yellow and beige dyes, respectively [4]. Wood is used in house construction and to make furniture and

bows. The young twigs are used as chew sticks for dental hygiene. *Z. usambarense* is also used as a "life" fence.

Previous studies have indicated that the extracts of *Z. usambarense* show antimalarial activity in an animal model [1]. Different extracts of the stem bark and the root bark exhibited significant antibacterial activities against Bacillus subtilis, Micrococcus luteus, and Staphylococcus aureus. The hexane, methanol, and water extracts of the leaves, root bark, and stem bark showed significant anti-inflammatory activity [5] in the cyclooxygenase (COX-1) assay.

Experimental Section

Zanthoxylum usambarense roots were collected from Soy location, in Elgeyo Marakwet County (Kenya). It was identified by Mr. Tuei at the University of Kabianga (UoK). A voucher specimen number *ZU 01* was deposited at UoK's herbarium. The roots were washed using tap water to remove dirt, chopped into small pieces, and then dried under the shade. The dried samples were ground to powder using mortar and pestle.

Organic Extraction

About 500g of the powdered plant material was extracted successively with dichloromethane (DCM) and methanol (MeOH) at a ratio of 1:1 (v/v) and MeOH, respectively. Extraction with MeOH took 48 hours while that of DCM took 24 hours. The extracts obtained were decanted and filtered through Whatman No.1 filter paper. The resulting filtrates were concentrated using a rotary evaporator yielding solid crude organic extracts.

Column Chromatography

The crude extracts from the root bark of *Z. usambarense* were separated on silica gel column chromatography [6]. The extracts were dissolved in just enough distilled solvents to form a slurry-like paste before loading on an evenly packed chromatographic column using clean pipettes. Thin-layer Chromatography (TLC) [6] was performed to determine the solvent system to be used for separation on column chromatography; [6] a 30:70 (v/v) mixture of hexane:ethyl acetate (EtOAc) gave the best separation. The column was then eluded with the identified solvent system yielding four fractions based on TLC analysis: F1 (23.20 mg), F2 (40.3 mg), F3 (56.78 mg), and F4 (100.05 mg). On further purification through chromatography, F2 yielded two white crystals (compounds 1 and 2). Fraction 4 was further purified using EtOAc in hexane in the ratio 20:80 (v/v) to yield compound 3.

Phytochemical analysis

Table 1: NMR Data for Compound 1.

S/N	^{13}C δ_C (ppm)	DEPT	HSQC δ_H (ppm)	HMBC
2	174	C		
3	48.7	CH	2.65	2,4,7,8
4	71.9	CH	3.55	3,5
5	158	C	-	-
6	90.2	CH_2	4.66, 4.91	4,5
7	24.3	CH_2	1.59	3,8
8	27.2	CH_2	2.07, 1.50	7
9	29.4	CH_2	1.32	10
10	29.7	CH_2	1.3	
11	29.7	CH_2	1.3	
12	29.7	CH_2	1.3	
13	29.7	CH_2	1.3	
14	29.7	CH_2	1.3	
15	29.7	CH_2	1.3	
16	29.7	CH_2	1.3	
17	29.7	CH_2	1.3	
18	29.7	CH_2	1.3	
19	29.7	CH_2	1.3	
20	31.5	CH_2	1.84, 1.51	19,21
21	22.6	CH_2	1.32	22,19
22	14.1	CH_2	0.91	20,21

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Structural elucidation using NMR and mass spectrometry

Characterization and structure determination was done using spectroscopic methods. Structure determination and mass analysis were done using Nuclear Magnetic Resonance (NMR [9,10] spectroscopy and Mass Spectrometry (MS), [11] respectively.

All 1D and 2D NMR spectra [10,12] were recorded on a Bruker Avance 500 MHz NMR spectrometer. [13] Samples were dissolved in deuterated chloroform before loading onto an NMR probe and acquiring data. Tetramethylsilane (TMS) was used as an internal standard and the chemical shift was reported as δ (ppm). The off-diagonal elements were used to identify the spin-spin coupling interactions in the 1H-1H Correlation spectroscopy (COSY) [14]. The proton-carbon connectivity, up to three bonds away, was determined using ^{1}H-^{13}C Heteronuclear Multiple Bonds Coherence (HMBC), [6] whereas Heteronuclear Single Quantum Coherence (HSQC) [15] was used to determine the connectivity of hydrogen to their respective carbon atoms.

Mass spectrometry

The mass spectra [11] for all pure compounds were recorded on Finnigan Tipple Stage Quadrupol Spectrometer (TSQ-70) with electron spray ionization (ESI) method in the analysis. Thermo Xcalibur Qual computer software [16] was used in the analysis of the mass chromatograms.

Bioassays

Pure standard isolates of Staphylococcus aureus [17] were cultured at UoK's microbiology laboratory and used for evaluating the antimicrobial activity of extracts and pure compounds isolated from *Z. usambarense*.

Antimicrobial bioassays

Antimicrobial activity of the extract from *Z. usambarense* was carried out using disc diffusion method [18]. Sterile filter paper discs (5 mm in diameter, Whatman No.1) were individually loaded with 30 microlitres of tested extract at a concentration of 0.1 gm/ml, 0.01 gm/ml, 0.001 gm/ml and were dried. After incubation, the antimicrobial activity was evaluated by measuring the inhibition zones (including the diameter of the discs).

Results And Discussion

Compound 1 was obtained as a yellow solid. Its mass was established to be 388 amu, based on HREIMS data, [7] corresponding to a molecular formula of $C_{21}H_{24}O_7$, which indicates a double bond equivalence [19] of 3, one being due to the furanyl ring, one being due to the carbonyl group and one to exo methylenic double bond [7] attached to furanyl skeleton. The Infrared (IR) [20] spectrum showed a carbonyl stretching band at 1705 cm^{-1} and a hydroxyl absorption band at 3364 cm^{-1}. This compound was identified as a furanyl group based on its characteristic ^{1}H NMR spectral pattern.

1H NMR spectrum showed resonance at δ_H 3.55 attributed to a methine proton in close proximity to a hydroxyl group H-4. Another methine resonance in the furan ring was observed at δ_H 2.66 H-3; this position was confirmed by HMBC correlation of H-3 to C-7 and C-4. Also present were the exo methylenic protons resonating at δ_H 4.66, 4.91 (H-6), these protons correlated with C-4 and C-5 in the HMBC spectrum. The long aliphatic chain of methylene protons was observed as overlapping peaks between δ_H 1.30- 2.07 (H-7 to H-21). Methyl peak was observed at δ_H 0.91 attributed to H-22 at the tail end of the methylene chain.

The 13_C spectrum exhibited the presence of 21 carbon resonances, one methyl (CH_3) peak, 16 methylene (CH_2), 2 methine (CH) carbons, and two fully substituted (quaternary) carbons.

Structure determination

Fraction 2 obtained from DCM:MeOH (1:1 v/v) solvent in column chromatography yielded two compounds after series of purification on 30:70 (v/v) of hexane:ethyl acetate (EtOAc) and later on isocratic solvent containing a mixture of EtOAc and hexane.

Compounds 1 and 2 were isolated both as white solids at room temperature. They were identified as structural isomers having the same molecular weight but a different order of attachments (Figure 1 & 2). The NMR data for compounds 1 and 2 are similar with slight difference of the absorption of C-2 (δ_C 174.0), C-5 (δ_C 158.0) for compound 1, and C-2 (δ_C 168.0), C-5 (δ_C 159.0), for compound 2. The slight variation in 13_C of the compounds is attributed to the resonance effects which in compound 1, a deshielded C-2 is created while a shielded electron rich C-2 is created due to resonance; these two effects then made carbons in furan ring of compound 1 absorbs up field while those of compound 2 absorbing downfield.

The connection of the two compounds to the hexadecyl group was determined using the HMBC correlations of H-3 (δ_H 2.65) to C-7 and C-8 for compound 1 and H-4 (δ_H 2.88) to C-7 in compound 2, respectively.

Additional NMR data for compounds 1 and 2 are shown in Figure 1 & 2 and Table 1 & 2, respectively. Based on these data, compound 1 was assigned the IUPAC name 3-hexadecyl-dihydro-4-hydroxy-5-methylenefuran-2(3H)-one while compound 2 was assigned the IUPAC name 4-hexadecyl-dihydro-3-hydroxy-5-methylenefuran-2(3H)-one. The two compounds are structural isomers with differences in the attachment of the hexadecyl site chain and the positions of the ketone functional group as well as that of the exocyclic double bonds. The two compounds are reported for the first time and hence considered to be new.

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Table 2: NMR Data for Compound 2.

S/N	13C δ_C (ppm)	DEPT	HSQC δ_H (ppm)	HMBC
2	168	C		
3	87	CH	4.88	2,4
4	40	CH	2.88	2,3,4,7
5	159	C	-	-
6	90.2	CH_2	4.66, 4.91	5
7	24.3	CH_2	1.59	3,8
8	27.2	CH_2	2.07, 1.50	7
9	29.4	CH_2	1.32	10
10	29.7	CH_2	1.3	
11	29.7	CH_2	1.3	
12	29.7	CH_2	1.3	
13	29.7	CH_2	1.3	
14	29.7	CH_2	1.3	
15	29.7	CH_2	1.3	
16	29.7	CH_2	1.3	
17	29.7	CH_2	1.3	
18	29.7	CH_2	1.3	
19	29.7	CH_2	1.3	
20	31.5	CH_2	1.84, 1.51	19,21
21	22.6	CH_2	1.32	22,19
22	14.1	CH_3	0.91	20,21

Table 3: NMR Data for Compound 3.

	^{13}C	DEPT	HSQC	HMBC	COSY
1.	127.5	C	-	-	-
2.	111.6	CH	7.26	1,3,6,7	-
3.	149.2	C	-	-	-
4.	147.5	C	-	-	-
5.	115	CH	6.9	3,4,6	6
6.	129.7	CH	6.92	1,4,5	5
7.	144.9	CH	7.45	1,2,8,9	8
8.	119.2	CH	6.33	1,7,9	7
9.	209.4	C	-	-	-
O-CH_3	51.6	CH_3	3.79	3	-

The two compounds (1&2) are furan derivatives having site chain attachment of saturated alkane as well as hydroxy, ketone, and exocyclic double bounds within the furan system. Formerly, spiculisporic acid B, spiculisporic acid C, spiculisporic acid, and secospiculisporic acid were isolated from the fungus Aspergillus fumigatu. These furan derivatives possess anti-inflammatory, anti-microbial as well as anti-cancer activities [21]. On the other hand, Chan et al (2017) [22] isolated six new furan derivatives from the fungal fermentation of Coriolopsis sp on solid rice media, the compounds were assigned the following IUPAC [23,24] names: 5-(3-methoxy-3-oxopropyl)-furan-2-carboxylic acid, 1-(5-(2-hydroxypropanoyl) furan-2-yl)-pentan-3-one, 2-hydroxy-1-(5-(1-hydroxypentyl)-furan-2-yl)-propan-1-one, 1-(5-(1,2-dihydroxypropyl)-furan-2-yl)-pentan-1-one,5-(1-hydroxypent-4-en-1-yl)-furan-2-carboxylic acid, and 5-(3-hydroxypentyl)-furan-2-carboxylic acid. The six isolated compounds showed

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no antimicrobial activities against Staphylococcus aureus (ATCC51650), *Ralstonia solanacearum, Fusarium oxysporum f. sp. cubense race 4, Fusarium oxysporum f. sp. niveum, Fusarium oxysporum f. sp. vasinfectum*, and *Candida albicans* (ATCC10231).

The diversity of the furan-based [25] natural products could be attributed to the flexibility of the 5-membered ring to accept site attachments as well as its reactive nature [26]. In the present study, the isolated compounds are new and hence provide useful information. This study then shows diverse sources of furan-based natural products [26] (Figure 3).

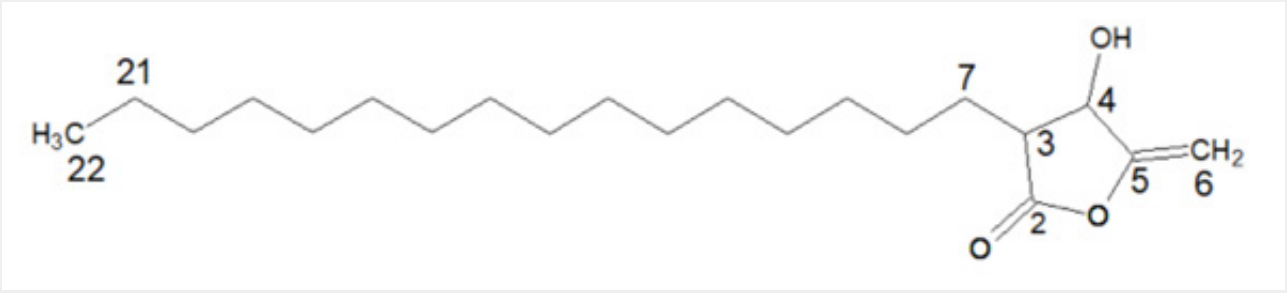

Figure 1: Compound 1.

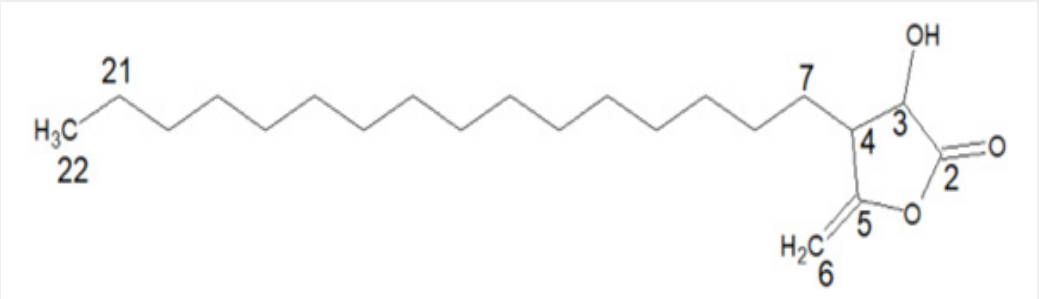

Figure 2: Compound 2.

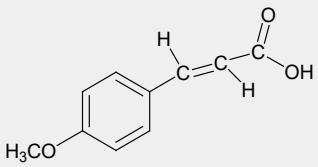

Figure 3: Compound 3: Fraction 1 yielded one pure compound (*trans-ferullate*) which appeared as a white crystalline at room temperature.

The crude extract obtained in MeOH:DCM (1:1 v/v) solvent system was purified in column chromatography using DCM:EtOAc (20:80 v/v) which resulted in Fraction 1 (F1). A white solid that crystalized at room temperature was analyzed using NMR and Mass spectrometers. It was found to be compound 3 (*trans-ferullate*). The molecular mass of 3 was established to be 194.18 amu, with molecular formulae of C10H10O4. This indicates a hydrogen deficiency index (HDI) [19] of 5, attributed to the three (3) conjugated double bonds in the benzene ring, a trans double bond on the side chain and carbonyl carbon of the carboxylic acid moiety (C-9). Compound 3 was identified as a *trans-ferulate* [27] bearing the methoxy and hydroxyl groups on the phenyl ring at positions 3 and 4, respectively. The 1H NMR spectrum indicates the presence of benzylic protons resonating at δ_H 7.26 (H-2), δ_H 6.90 (H-5), and δ_H 6.92 (H-6) corresponding to carbon signals at δ_C 111.6 (C-2), δ_C 115.0 (C-5) and δ_C 129.7 (C-6) in the HSQC spectrum. Also present are the methylene protons with varied multiplicities at δ_H 7.45 (H-7) and δ_H 6.33 (H-8) corresponding to carbon signals at δ_C 144.9 (C-7) and δ_C 119.2 in HSQC spectrum. Methoxy protons were observed at δ_H 3.79, corresponding to the

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carbon signal at δ_C 51.6 in the HSQC spectrum. Additionally, a hydroxyl proton resonating at δ_H 5.30 was observed.

The 13C NMR and DEPT [6,28] spectra show that compound 3 has a total of 10 carbons, 5 methine carbons resonating at δ_C 111.6 (C-2), δ_C 115.0 (C-5), δ_C 129.7 (C-6), δ_C 144.9 (C-7) and δ_C 119.2 (C-8). Three quaternary carbons at δ_C 129.5 (C-1), δ_C 149.2 (C-3), and δ_C 147.5 (C-4). One carbonyl carbon resonating at δ_C 209.4 (C-9) and a methoxy carbon at δ_C 51.6.

The HMBC [12] spectrum showed that proton resonating at δ_H 7.26 (H-2) correlates with carbon signals; C-1, C-3, and C-6. Consequently, proton resonating at δ_H 6.90 (H-5) correlates with carbon signals; C-3, C-4, and C-6. Also observed in the HMBC spectrum was a strong correlation between methoxy protons resonating at δ_H 3.79 and carbon signal at δ_C 149.2 (C-3). In the ^{1}H-^{1}H COSY [6] spectrum correlations between proton at δ_H 6.90 (H-5) with that at δ_H 6.92 (H-6) were observed. Also, olefinic protons at δ_H 7.45 (H-7) and δ_H 6.33(H-8) correlated. Other HMBC and COSY spectra are shown in Figure 4. Compound 3 was assigned IUPAC and common names, (E)-3-(4-hydroxy-3-methoxyphenyl) acrylic acid and trans-ferulate, respectively.

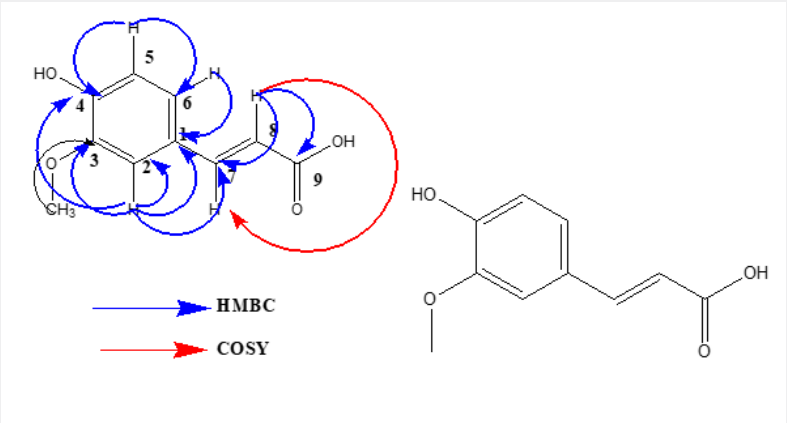

Figure 4: HMBC and ^{1}H-^{1}H COSY Correlations of Compound 3.

Compound 3 is a cinnamic acid derivative having both methoxy and hydroxy substituents on the phenyl and is generally referred to as ferulic acids. The insecticidal activity of compound 3 has been attributed to the conjugation in the benzene rings as well as the activation caused by the ring activators (-OH and -OCH_3 groups) on the benzene ring [29]. Consequently, the trans double bond on the side chain of the carboxylic acid moiety offers greater reactive stability to the compound which can be used as an insecticide or a precursor in synthesizing bioactive compounds (Table 3).

As part of an ongoing NSF-funded "Undergraduate Student Achievers in Research (USTAR) Program at Missouri State University-West Plains (MSU-WP), one of the end-of-semester exit survey questions posed by faculty to students in STEM-eligible disciplines [30] is, "How can the STEM faculty motivate undergraduate/graduate students to participate in research?" While the responses from undergraduates are usually varied, the two most common responses emphasize: 1) the need for scholarships, academic support services, and mentoring programs that promote student participation in on-campus faculty-led research instead of working at local "stores" (e.g., flipping burgers at Burger King), and 2) the need for interesting and cutting-edge research projects that are not only inspiring but also full of the "Aha" moments. Some students go even further and indicate that "inspiring" research should involve beautiful "colored chemical reactions" or spectacular "crystalline compounds."

The collaborating faculty members from MSU-WP and the University of Kabianga (UoK) unanimously selected natural products research to inspire undergraduate and graduate students. [6,31] Natural products cut across many scientific disciplines such as organic chemistry, analytical chemistry, biochemistry, botany, microbiology, and other chemical sciences. Moreover, the isolation, chemical modifications, structural elucidation, and bio-testing of natural products promote high-impact practices [32] (i.e., first-year seminars, engaged student learning communities, undergraduate/graduate research, service-learning, and capstone experiences). To inspire students and create many WOW! Moments in faculty-led natural products research, we use an industry [33] model. For fun and to enhance personal ownership of the projects, students in each research group are told to imagine as if they are part of a new startup company called Plants Pharmaceutical Company. Students would be the employees while the faculty members would be the presidents. The goal of the new pharmaceutical company is to make money by developing new and legal plant-based drugs. The employees need to work as a team and must understand how drugs work, how targets and lead compounds are identified, how they are optimized, how clinical trials are conducted, intellectual property rights, and issues surrounding patents.

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To meet the goals of the new pharmaceutical company, the employees write five-page capstone natural products research proposals. [34] Each team develops a grant proposal requesting a "theoretical" two million dollars in funds to support their research project. The proposal will contain the following components: (1) An outline of the research plan stating: a hypothesis, research question(s), and weekly schedules for the entire semester; (2) Annotated bibliography of literature search using ACS citation format [35] and the Japanese KENSHU Method; [36] (3) A list of special glassware, equipment, MSDS of chemicals, reaction schemes, budget and justification, purification schemes, and product identification schemes; (4) How barrier banding protocols will be implemented to prevent lab-related exposure to COVID-19; (5) Experimental procedures for bio-testing of natural products against various biological targets; (6) A five-PowerPoint slide oral presentation [37] summarizing the proposal; and (7) faculty member's approval signature.

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