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Antimicrobial Evaluation of Cardol and Cardol-Metal Complexes from the Nut Shell Liquid of *Anacardium occidentale*

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ABSTRACT

Cardol, as one of the major constituents of Cashew Nut Shell Liquids has received little attention in terms of modification and applications. The presence of two hydroxyl groups and an alkyl side chain of 15 carbon length make it a natural compound of interest. The present study is aimed at modification and complexation of cardol, and the antimicrobial investigations of the compound as well as its analogue and complexes. Isolated cardol from cashew nut shell liquid was nitrated, and the compounds were used in the synthesis of metal (II) complexes of Copper, Cobalt, and Zinc. The compounds and complexes were characterised by melting points, UV-Vis spectrophotometry, Fourier Transform Infrared (FTIR) spectrophotometry, and Nuclear Magnetic resonance (NMR) spectroscopy. The antibacterial and antifungal evaluations of both the compounds and complexes were tested *in vitro* against some selected bacteria and fungi. From the results, Copper complex of nitrocardol produced significantly higher antibacterial zone of inhibition (11.5 ± 2.1 mm) against *Pedobacter mendelii* than tetracycline while Copper complex of cardol showed significantly higher antifungal activity (13.5 ± 2.1 mm) against *Rhizopus stolonifar* than clotrimazole (10.0 ± 0.0 mm). It was generally observed that modification and metal complexation enhanced the antimicrobial activity of cardol. Further studies on these complexes could be done to enhance their potencies and potentials for use as antibacterial and antifungal agents.

Keywords: *Anacardium occidentale*, Cardol, Antifungal, Antibacterial, Complex

Introduction

Several attempts have been made towards complexation of natural products in order to enhance their solubility, bioavailability as well as increasing their pharmacological effects.[1] One of the key areas of research in bioinorganic chemistry is the application of metal ions or metal ion-binding compounds to biological systems for the treatment of diseases.[2] Natural products are used to form metal complexes because it has been found that addition of transition metals to already biologically active natural products increases their therapeutic activity, improves their effectiveness and minimizes their adverse effects.[3]
Decarboxylation of anacardic acid from technical cashew nut shell liquid (CNSL) at elevated temperatures of over 180ºC produced basically cardol (20%) and cardanol (65%).[4,5] Not many works have been reported on cardol among the constituents of cashew nut shell liquid (CNSL). Lomonaco *et al*., reported the larvicidal activity of CNSL with cardol being the most active.[6] Also, Cardol monophosphate, cardol diphosphate and cardol phosphorothioate were synthesized by Almenda *et al*.[7], their efficiencies and mode of actions as larvicides and acetylcholinesterase (AChE) inhibitors of *Aedes aegypti* were evaluated, and they showed excellent activity. Mostly, transition metals like Fe, Co, Zn and Cu are used for complex formation because it is assumed that anticancer medications based on these endogenous metals are less harmful than their platinum equivalents.[8]

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Most metal complexes have been found to have antibacterial and antifungal properties and, in most cases, better than their ligands.[9,10] Other activities of natural metal complexes include anticancer, antimicrobial, antirheumatic/antiarthritic, antioxidant, and anti-inflammatory activities.[11] The antioxidant properties of cardanol and cardol, two components of technical CNSL has been established by electrochemical and computational methods where they demonstrated better activity compared to the commercially available products.[12] The amphiphilic antioxidant properties of cardol and cardanol derivatives have also been established by examining how well they can prevent an oxidizable organic substrate from undergoing autoxidation.[13] Oke *et al*. also reported anacardic acid to have both bacterial and antifungal effects.[10] CNSL on the other hand, has been shown to exhibit growth inhibitory and bactericidal effects against four strains of streptococcus and *Enterococcus faecalis*.[14] Quantitative and qualitative variations which arises as a result of differences in the extraction methods of plants have direct influences on the antibacterial activity of an extract.[15] A study by Ashraf and Rathinasamy, revealed the antiproliferative effect of purified CNSL against cancer cells with no harmful effect on normal cells.[16] The study revealed that purified CNSL also have strong antibacterial and wound-healing properties, and this has been shown to be extremely helpful in treating patients with long-term wounds.[16]
The present research therefore is aimed at improving the therapeutic value of cardol through its synthetic modification and complexation, and investigating the antibacterial and antifungal activities of the modified compounds as well as their complexes with the possibility of their use as antimicrobial agents.

Materials and Methods

Sample Collection and Preparation

Nuts of *Anacardium occidentale* were purchased in April 2019 from Osogbo, Osun State, Nigeria. They were authenticated at the Bowen University Herbarium and voucher specimen with voucher number BUH031 was deposited.

The nuts were handpicked from the shells after being sun-dried for two weeks. In order to create easily extractable surfaces, the split shells were further sun-dried for few days. The oil was extracted from the crushed shells (789 g) by macerating them in methanol (1.5 L) for 72 hours. The concentrated oil was placed in a fume cupboard until it was used.[10]

Isolation of cardol

Cardol was isolated using an established method.[17] About 200 g of the extracted shell oil was liquefied in 1200 mL of aqueous methanol. To the mixture was added 100 g of calcium hydroxide in portions under constant stirring until all have been added. Next, the mixture was swirled at about 50ºC for three hours. The calcium anacardate that was precipitated out was filtered and washed with 400 mL methanol. The solid material was put aside. The solution obtained after the above filtration was concentrated with rotary evaporator to about 400 mL. Ammonium hydroxide solution (25%, 400 mL) was added to the concentrate and stirred for about 15 minutes, after which it was extracted three times with 200 mL each with a mixture of ethyl acetate and hexane in the ratio 2:98. The mixed organic layers were washed with 200 mL solution of sodium hydroxide and 200 mL distilled water, respectively. The resultant organic layer was dried with sodium sulphate and concentrated to get 20 g of cardanol. The methanol ammonia solution was again extracted with 400 mL of the same mixture of solvents (ethyl acetate and hexane) in the ratio 80:20. The extract was then washed with 200 mL 5% hydrochloric acid followed by same amount of distilled water. The product was concentrated and further dried with sodium sulphate to give a dark pink cardol (40 g).[18] The product was purified with column chromatography.[19] The column was packed with a slurry of silica gel until it was three quarter full and without cracks. White sand was added to the top of the packed column before the extract was introduced. The column was eluted with solvent mixture at different ratios to give pure cardol. The purified product (cardol) was characterised by Cary 630 FTIR (Agilent Technologies) and Bruker Technologies 400 MHz ^{1}H-NMR, and 100 MHz ^{13}C-NMR.

Nitration of Cardol

This was done according to the method described by Vogel.[20] Briefly, a mixture of 50% nitric and sulphuric acids (25 mL each) was added slowly to 2.3 g of sample and stirred for about 2.5 hours at 60-70ºC. The product was brought to room temperature, diluted with ice water and extracted with ethyl acetate (200 mL) to give 1.2 g of a yellow liquid (1.2 mL) which was characterised by Cary 630 FTIR (Agilent Technologies) and Bruker Technologies 400 MHz ^{1}H-NMR, and 100 MHz ^{13}C-NMR as nitrocardol.

Formation of metal (II) complexes of cardol and nitrocardol

Metal complexes were synthesised using cobalt chloride hexahydrate, copper sulphate pentahydrate, and zinc acetate dihydrate using a modified method of Mendes *et al.*[21] Cardol (C_2), together with its nitrated compound were used as binders at a stoichiometric ratio of 1:1 under constant magnetic stirring.

Synthesis of copper II sulphate pentahydrate complex of cardol (C_2-Cu)

C_1 (1.0 g) was dissolved with 10 mL methanol in a 50 mL beaker. Copper (II) sulphate (0.70 g) was dissolved in the solution and stirred for 180 min. Ammonium hydroxide was added to the solution to raise its pH to between 10 and 11 while maintaining a temperature of 55ºC. The solution was filtered, followed by a methanol wash (10 mL) after it was brought to room temperature. The complex formed was subsequently dried in a desiccator to give a brownish solid (0.81 g).[17]

Synthesis of cobalt (II) chloride hexahydrate complex of nitrocardol (NC_2-Co)

NC_2 (1.0 g) was dissolved with 10 mL methanol in a 50 mL beaker. Cobalt (II) chloride (0.36 g) was dissolved in the solution and stirred for 90 min. Ammonium hydroxide was added to the solution to raise its pH to between 10 and 11 while maintaining a temperature of 30ºC. The solution was filtered, followed by a methanol wash (10 mL) after it was brought to room temperature. The complex formed was subsequently dried in a desiccator to give a pinkish powder (0.05 g).[21]

Synthesis of copper (II) sulphate pentahydrate complex of nitrocardol (NC_2-Cu)

NC_2 (1.0 g) was dissolved with 10 mL methanol in a 50 mL beaker. Copper (II) sulphate (0.70 g) was dissolved in the solution and stirred for 180 min. Ammonium hydroxide was added to the solution to raise its pH to between 10 and 11 while maintaining a temperature of 55ºC. The solution was filtered, followed by a methanol wash (10 mL) after it was brought to room temperature. The complex formed was subsequently dried in a desiccator to give a greenish pellet (0.30 g).[21]

Synthesis of Zinc (II) acetate dihydrate complex of nitrocardol (NC_2-Zn)

NC_2 (1.0 g) was dissolved with 10 mL methanol in a 50 mL beaker. Zinc (II) acetate (0.62 g) was dissolved in the solution and stirred for 90 min. Ammonium hydroxide was added to the solution to raise its pH to between 10 and 11 while maintaining a temperature of 30ºC. The solution was filtered, followed by a methanol wash (10 mL) after it was brought to room temperature. The complex formed was subsequently dried in a desiccator to give a dark brown pellet (0.05 g).[21]

In vitro Antibacterial Evaluation

The antibacterial assessments of cardol and its complexes were conducted according to the method previously described by Oke and Oluranti,[19] using bacterial isolates obtained from Bowen University Microbiology laboratory. The bacterial isolates used include four gram-positive: *Bacillus cereus* (obtained from food samples), *Enterococcus spp.*, *Bacillus cereus* (obtained from hospital wastewater), and *Bacillus subtilis*, and four gram-negative: *Cronobacter Sakazaki*, *Escherichia Coli*, *Pedobacter mendelii*, and *Enterobacter spp*.

In vitro Antifungal bioassay

Cardol and its complexes were tested for their antifungal properties following the method reported by Oke and Oluranti,[19] using fungal isolates from Bowen University's microbiology laboratory. The fungal isolates used were *Aspergillus flavus*, *Aspergillus fumigatus*, *Rhizopus stolonifer*, *Penicillium citrinum*, and *Aspergillus niger*

Results and Discussion

UV-Visible spectroscopy

Nitrocardol and its metal (II) complex of zinc in DMSO exhibited bathochromic shift in their UV-Vis absorption spectra compared to that of cardol (Table 1). This might be as a result of interactions between the metal and the hydroxyl group (OH) of cardol (C_2) resulting in an electronic redistribution between the free molecules and the metal ions thereby forming an extended ligand system.[22] However, the metal (II) complexes of copper (C_2-Cu and NC_2-Cu) showed an hypsochromic shift compared to that of cardol (C_2).

Table 1: UV-Visible spectral data of cardol, nitrocardol and the hydrated metal (II) complexes

Compound	λmax (nm)	Abs
C_2	278	0.215
C_2- Cu	259	3.179
NC_2	371	0.629
NC_2-Cu	264	0.576
NC_2-Zn	283	0.501
NC_2-Co	-	-

FTIR spectra of cardol and its complexes

Cardol (C_2) showed a broad absorption band for hydroxyl (OH) group at 3343 cm^{-1}, this broad band could be attributed to the double OH groups on its benzene ring. The aromatic C-H band was at 3009 cm^{-1} while the bands for C=C (aromatic), C=C (aliphatic) and C=O showed at 1595 cm^{-1}, 1459 cm^{-1}, and 1146 cm^{-1}, respectively. The bands for C_2-Cu deviated from that of C_2 as expected; the -OH band shifted up field to 3477 cm^{-1}, while the bands for -C=C (aromatic), -C=C (aliphatic) and -C=O showed at 1669 cm^{-1}, 1457 cm^{-1}, and 1064 cm^{-1}, respectively. The shifts in bands are due to the complex formation on the C_2 ring.

Nitrocardol (NC_2) showed its absorption band for OH at 3395 cm^{-1}, while the bands for C=C (aromatic), C=C (aliphatic) and C=O were observed at 1628 cm^{-1}, 1438 cm^{-1}, and 1172 cm^{-1}, respectively. The reason for these shifts is the introduction of a nitro group which was represented by the band at 1545 cm^{-1}. For NC_2-Cu, the OH band shifted down field from that of NC_2 to 3472 cm^{-1}, while the bands for C=O, aliphatic C=C, and aromatic C=C showed at 1362 cm^{-1}, 1319 cm^{-1} and 1636 cm^{-1}, respectively. These changes are due to the formation of new Cu(II) bonds with that of nitrogen atom of the nitrocardol which explains the disappearance of the nitro absorption band in the spectrum. The zinc (II) complex of NC_2 (NC_2-Zn) showed absorption spectrum deviations from that of NC_2 and NC_2-Cu; the spectrum gave the following absorption bands at: 3345 cm^{-1} (OH), 1619 cm^{-1} (C=C aromatic), 1360 cm^{-1} (C=C aliphatic) and 1313 cm^{-1} (C-O). The appearance of a band at 1546 cm^{-1} is an indication of the presence of NO_2 which implies that the complex was not formed with nitrogen atom as presented in Figures 1 and 2.

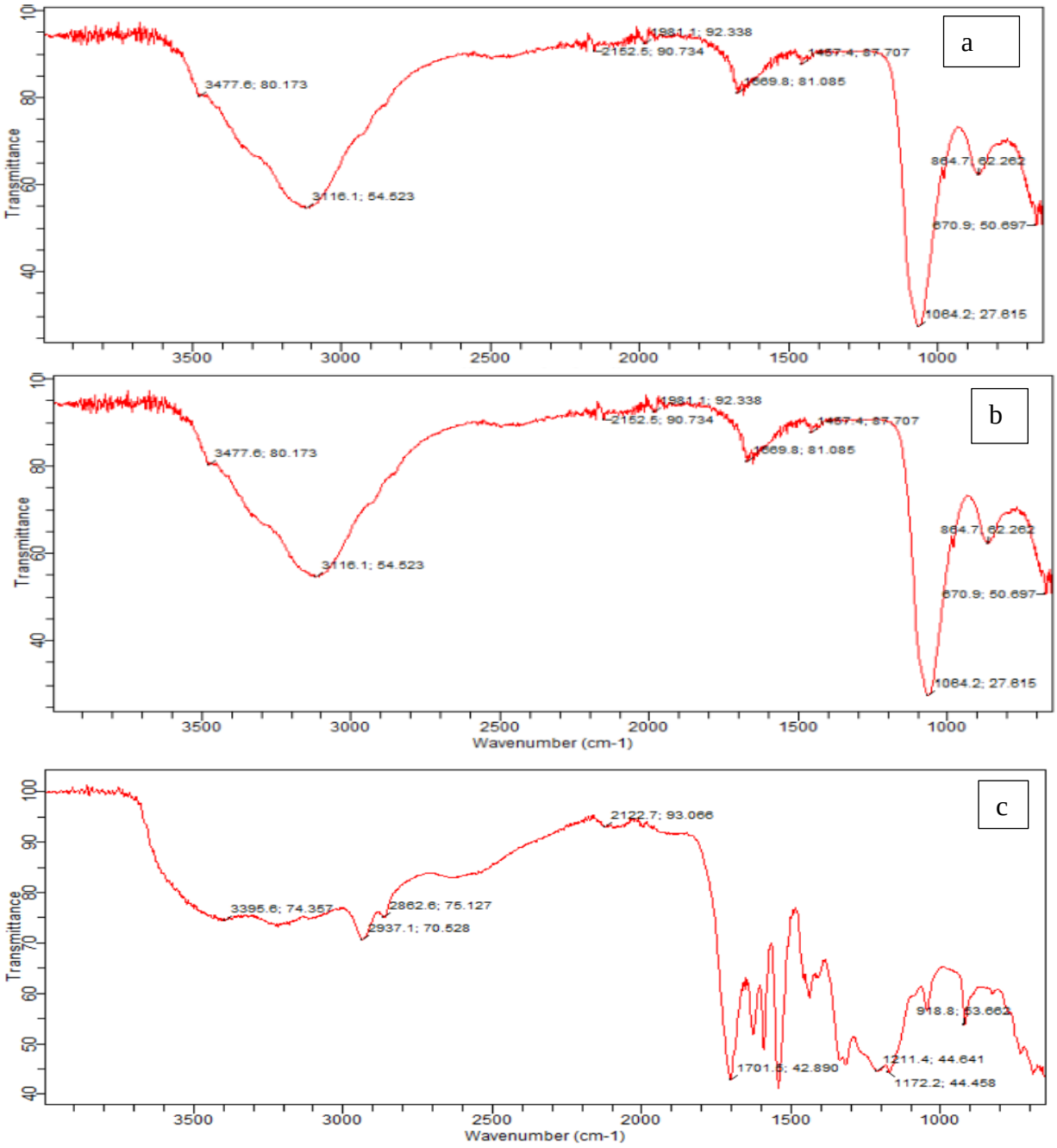

Figure 1: FTIR spectra of (a) C_2, (b) C_2-Cu and (c) NC_2

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NMR spectra of cardol and nitrocardol

The ^{1}H-NMR spectrum for C_2 presents signals at 8.84 ppm which indicates the two -OH protons of the cardol ring. The signals at 6.76 ppm, and 6.31 ppm represents the three protons on the cardol ring. The signals between 4.72 - 5.79 ppm represent alkene protons. The benzylic protons appear at 3.42 ppm. Other signals represent the remaining protons on the alkyl side chain. For the ^{13}C-NMR, the signal at 158 ppm represents the carbons bearing the OH groups, the signal at 144.64 ppm represents the carbon of the alkyl side chain while the signal at 106 ppm represents the remaining carbon atoms on the cardol ring. The signals between 100.42 - 137.02 ppm represent alkene carbons while the remaining signals between 13.98 - 35.81 ppm represent the saturated carbon atoms on the alkyl side chain.

Cardol (C_2)

C_2 was isolated as a dark pink liquid with UV (DMSO) λmax = 278 nm; FTIR (ν, cm^{-1}): 3343 (OH), 3009, 2853 and 2924 (CH), 1595 (aromatic C=C), 1459 (aliphatic C=C), 1146 (C-O) cm^{-1}; ^{1}H-NMR and ^{13}C-NMR present signals as shown below:

^{1}H-NMR (400 MHz, DMSO-*d6*) δ 8.84 (s, 2H), 6.76 (q, *J* = 9.6, 7.9 Hz, 1H), 6.31 (d, *J* = 6.4 Hz, 2H), 5.79 (d, *J* = 7.9 Hz, 3H), 5.51 (ddd, *J* = 16.6, 11.0, 5.4 Hz, 1H), 5.07 (dtd, *J* = 26.5, 11.8, 10.8, 6.3 Hz, 5H), 4.72 (dd, *J* = 24.4, 13.5 Hz, 2H), 3.52 (s, 1H), 3.53 – 3.36 (m, 6H), 2.50 (dd, *J* = 13.9, 6.8 Hz, 4H), 2.10 (t, *J* = 7.7 Hz, 2H), 1.76 (d, *J* = 6.4 Hz, 1H), 1.73 (d, *J* = 7.1 Hz, 2H), 1.68 (d, *J* = 17.0 Hz, 1H), 1.23 (p, *J* = 6.9 Hz, 3H), 1.07 (dd, *J* = 14.6, 7.3 Hz, 2H), 1.00 (s, 12H), 0.96 (s, 1H), 0.83 (s, 1H), 0.59 (q, *J* = 7.3 Hz, 2H).

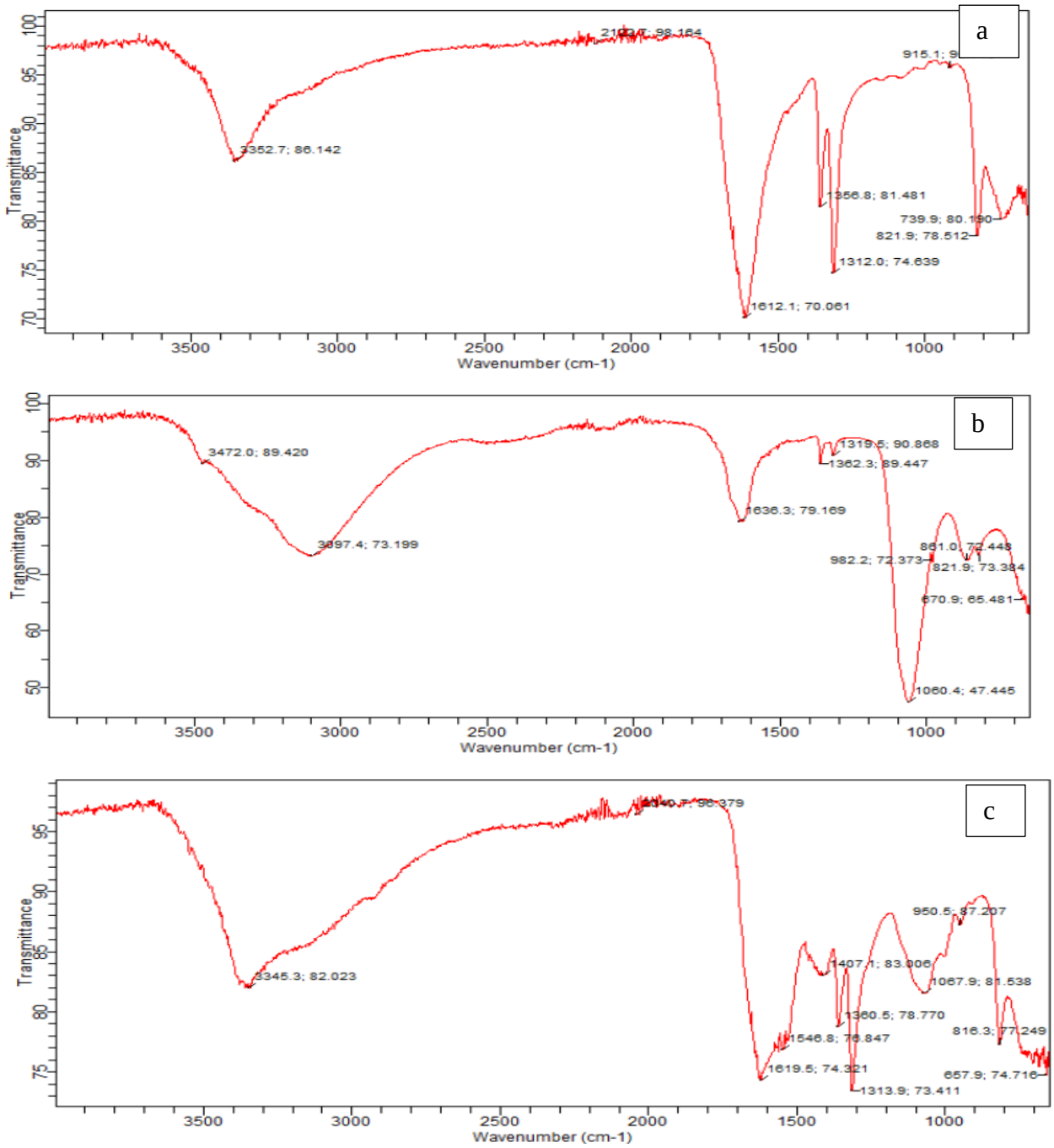

Figure 2: FTIR spectra of (a) NC_2-Co (b) NC_2-Cu and (c) NC_2-Zn

^{13}C-NMR (100 MHz, DMSO-*d6*) δ 158.60, 144.64, 137.02, 130.63 – 129.31 (m), 128.32, 128.11, 127.81, 126.87, 115.16, 106.73, 100.42, 35.81 (d, J = 12.8 Hz), 31.79 (d, J = 16.7 Hz), 31.39 (d, J = 14.8 Hz), 29.61 (d, J = 7.7 Hz), 29.25 (dd, J = 13.0, 5.3 Hz), 27.12, 25.63 (d, J = 7.4 Hz), 22.69 (d, J = 9.4 Hz), 14.32, 13.98.

NC_2 was synthesised as a yellow liquid with UV (DMSO) λmax = 371 nm, FTIR (ν, cm^{-1}): 3395 (OH), 3210, 2862 and 2937 (CH), 1628 (aromatic C=C), 1438 (aliphatic C=C), 1546 (NO_2), 1172 (C-O) cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-*d6*) shows signals at δ 8.67 ppm and 8.51 ppm which could be attributed to the protons of the two –OH groups which show a slight difference from that of C_2 due to the introduction of nitro groups on the ring. There was no signal for aromatic proton which could be due to the nitro groups occupying the positions giving a possible trinitrocardol. The signals between 5.37 ppm and 5.52 ppm are attributed to the alkene and benzylic protons, while the remaining protons on the alkyl side chain are shown by the signals from 1.17 ppm to 2.51 ppm. The ^{13}C-NMR spectrum displayed signals as given below: ^{13}C-NMR (100 MHz, DMSO-*d6*) δ 176.77 – 174.51 (m), 172.08, 161.19, 148.92, 136.27 – 134.01 (m), 126.36 (d, J = 94.0 Hz), 34.09 – 33.75 (m), 28.41 (d, J = 15.1 Hz), 24.27, 21.71, 20.16, 11.54.

Physical Properties

The physical properties and percentage yields of cardol, nitrocardol and their complexes are shown in Table 2.

Antibacterial Activity

Cardol recorded very good activity against all the four gram-positive bacteria tested. Although, the activity was less than that of tetracycline which was the standard drug used. C_2 did not show any activity against all the gram-negative organisms. All the gram-positive bacteria showed some resistance to C_2-Cu and NC_2-Cu, NC_2-Cu showed activity against *pedobacter mendelii*, while NC_2-Zn was not active against any of the organisms tested. Figure 3 shows the histogram of these activities for the test compounds and standard drug (tetracycline).

Table 2: Physical properties of cardol, nitrocardol and their complexes

Compound	State	Colour	Yield (%)
C_2	liquid	dark pink	20
NC_2	liquid	yellow	52
NC_2-Co	powder	pinkish	5
NC_2-Cu	pellet	greenish	30
NC_2-Zn	pellet	dark brown	5

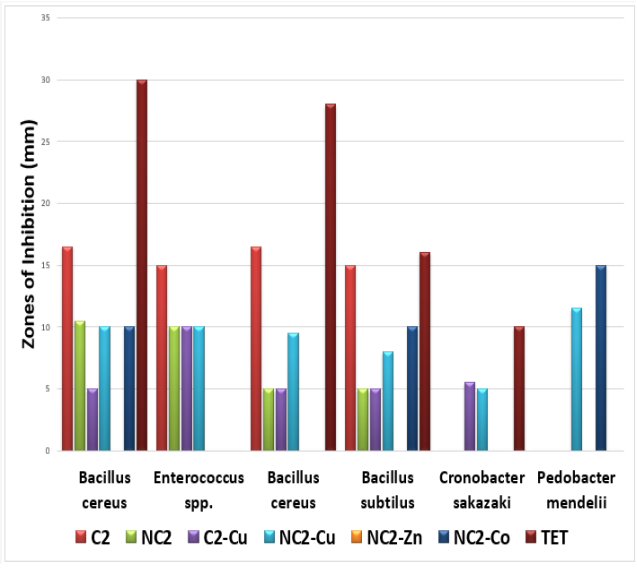

Figure 3: Antibacterial activity of cardol, nitrocardol and their hydrated metal (II) complexes.

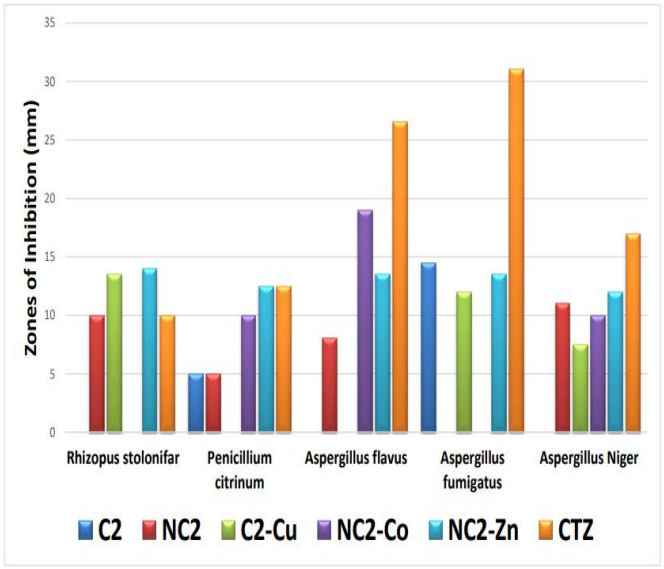

Figure 4: Antifungal activity of cardol, nitrocardol, and their hydrated metal (II) complexes.

Antifungal Activity

The cardol and nitrocardol complexes gave promising results (Figure 4). Against *Rhizopus stolonifar*, the copper (II) complexes of cardol and nitrocardol were outstanding with zones of inhibition of 13.5 ± 2.1 mm and 14.0 ± 0.0 mm, respectively which were better than that of clotrimazole the standard drug used with zone of inhibition of 10.0 ± 0.0 mm.

Conclusion

The isolated cardol and its nitro analogue (nitrocardol) were used for the synthesis of Zn^{II}, Co^{II}, and Cu^{II} complexes. The antibacterial activity recorded for C_2 and its complexes were fairly good. Their antifungal activity was significant, with copper (II) complexes of cardol and nitrocardol demonstrating outstanding results as shown by their significantly higher zones of inhibition (13.5 ± 2.1 mm and 14.0 ± 0.0 mm against *Rhizopus stolonifar* and *Penicillium citrinum*, respectively) than that of clotrimazole with zone of inhibition of 10.0 ± 0.0 mm. The findings from this study will serve as the basis for further studies on C_2 and its complexes with the purpose of improving their antibacterial and antifungal activities.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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