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Research Article

Metal and organic characterization of bladder stones removed surgically from VesicoVaginal Fistula patients at the National Obstetric Fistula Centre, Abakaliki, Ebonyi State

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Keywords: Whitfieldia lateritia; Vesicovaginal fistula; Bladder stones; Methenamine; Pentanethiol

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Abstract

Objectives: Complication of obstetric fistula is the formation of bladder stones which rarely occur in Vagina-Vesico Fistula (VVF) patients. In this study, the metal and organic characterization of bladder stones removed between 2010-2019 from vesicovaginal fistula patients managed at the National Obstetric Fistula Centre (NOFIC), Abakaliki, Ebonyi State, Nigeria were carried out.

Methods: The solubility of the bladder stones in different solvents were investigated and metal compositions were determined using Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OESS). The qualitative chemical composition was determined following standard procedures while the structural chemical characterization and functional groups were determined using the Gas Chromatography-Mass Spectrometry (GC-MS) and Fourier-Transform Infrared spectroscopy (FTIR).

Results: Distilled water and aqueous solvent chloroform extract of W. lateritia demonstrated significant capacity to dissolve bladder stones in-vitro. Chemical compounds identified include uric acid, oxalate, cysteine, and phosphate from the bladder stones. The metals found in the bladder stones were: Ca, Na, Cu, Zn, Mg, B, Pb, and Al. Trace elements can influence the external morphology of growing crystals and may increase or decrease the speed of the crystallization process. The GC-MS revealed the presence of the following compounds: methyl 2-Hydroxyethyl sulfoxide; methylene chloride; mercaptamine;1,1diethoxy, dichloroactealdehyde; Cyclopentasiloxane; monoammonium salt; di-Allo-Cystathionine; dichloroacetaldehyde; 2-(2Furyl)-2,5-dimethyltetrahydrofuran; Methenamine; 1,1-Difluoro-1-sila-5-thiacyclooctane; Triacetonetriperoxde; 4-Aminosalicylic acid, 3-Trimethylsilyl (3TMS) derivative;Pentanethiol; and 2,5-Bis-(5-hexyl-[1,3,2]dioxaborinan-2-yloxy)-benzene. FTIR revealed the following: hydroxyl, carboxylic, ester, aromatic, and aliphatic groups, confirming the compounds identified.

Conclusion: Metals (Mg, Ca, Pb, etc), organic metabolites (oxalate, cystine, uric acid, phosphate, methenamine, methylene chloride, 4-Aminosalicylic acid, 3-Trimethylsilyl, etc) were found in the bladder stones.

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Introduction

Vesicovaginal fistula (VVF) refers to abnormal communication between the bladder and the vagina resulting in continuous involuntary leakage of urine through the vagina [1,2]. It has enormous medico-social and psychological consequences [3,4]. The burden is reported to be highest in Africa and Asia with estimates of up to 2,000,000 in Africa alone [5]. Nigeria is reported to contribute 40% of the global burden of the disease with approximately 12,000 new cases per year [3]. The underlying factors include poverty, illiteracy, cultural practices, early marriage, obstructed labor, gynecologic surgery, and lack of access to quality maternity care [3,6]. The presence of bladder stones in patients with VVF may account for failed VVF repair, recurrent urinary tract infection, and possible pressure effects on the ureters and urethral with resultant complications, particularly in the face of a successful repair with stone in situ. VVF patients with stones are also more likely to undergo multiple surgical attempts at repair with obvious psychological and financial implications [2]. The formation of the bladder stones is often a result of reduced intake of fluid by the patient as a coping mechanism to reduce persistent wetness [7]. Bladder stones are hard crystal masses formed in the bladder by minerals and organic materials that are found in urine [8]. Bladder stone formation is affected by general systemic factors which influence the chemical compositions, physical properties of urine and urinary tract infections, environmental factors, as well as conditions of vesicovaginal fistula (VVF) [9]. Other factors include the degree of urine saturation with certain components and the presence of lithogenesis inhibitors and promoters [10,11]. The oxalate, uric acid, phosphate, cystine, and xanthine have been implicated in the bladder stone formation [10], which vary in their compositions [12]. Treatment of stone disease is a challenging issue for the healthcare organization [13]. Stone size and number, patient's history of treatment, general health status, and surgeon's preference are considered in therapeutic decisions [13]. Herbal materials with a diuretic, antispasmodic, and antioxidant activities exert inhibitory effects on crystallization, nucleation, and aggregation of crystals, making them useful for the treatment of stone [14]. The surgical removal of bladder stones either through the fistula vaginally or rarely through the suprapubic region has remained the basic treatment strategy for the affected VVF patients at National Obstetric Fistula Centre (NOFIC), Abakaliki, Ebonyi State. Futuristic efforts towards designing infusions that can dissolve the bladder stones in-vivo or at least reduce the size of bladder stones demand their chemical characterization. Also, bladder stones, although, have been characterized in other climes but evidence abounds on the compositional variability [9], both individually and geographically, hence the need to characterize the bladder stones from NOFIC, Abakaliki. To date, there has not been a report on the characteristics of bladder stones that occur in VVF patients in this region of South-Eastern, Nigeria and specifically patients managed by NOFIC. This study, therefore, was designed for the characterization of metal and organic compositions of bladder stones in vesicovaginal fistula patients.

Materials and methods

Study area

This study involved women with vesicovaginal fistula aged between 20-65, who were managed by the National Obstetric Fistula Centre, Abakaliki, Ebonyi State, Nigeria. NOFIC is a National Obstetric Fistula Reference Centre of excellence for the provision of free treatment, training, rehabilitation, research, and prevention.

The population of Ebonyi State is estimated to be about two million with women and girls aged 13years and above forming 52% of the population [15]. The National Demographic and Health Survey indicates that many of the women in Ebonyi State deliver their children at home and their lives are characterized by poverty, illiteracy, poor access to maternal care services and lack of access to basic social services, and enduring family violence [15] which expose them to high risk of VVF [2].

Collection of bladder stone samples

The bladder stones used for this preliminary study were part of the preserved twenty-four bladder stones collected by the lead surgeon in the Centre, Professor Ileogben Sunday-Adeoye collected over ten years from vesicovaginal fistula patients Figure 1.

Preparation of solvents used for solubility study

Fifty (50 g) each of *W. lateritia* and O*cimum gratissimum fresh* leaves was boiled separately for 10 mins at 70^{o}C in a 500ml capacity beaker containing100 ml of distilled water. It was cooled, decanted, and supernatants (each called *W. lateritia* leaf decoction-solvent 3 *and O. gratissimum* leaf decoction-solvent 6) stored in a clean bottle for use in the solubility analysis.

Ethanol soxhlet extract of the powdered *W. laterita* leaf (prepared by weighing 50g of the leaf into a round bottom flask containing 300 ml of ethanol, after being placed on the soxhlet apparatus, switched on, and allowed for 4hrs before being switched off, the flask was allowed to cool and then concentrated to paste using a rotary evaporator. The paste was used to prepare aqueous solvent (solvent 4) and oil solvent (solvent 5). This was done by dissolving 1 g of the *W.lateritia* leaf paste in 10 ml of water (solvent 1) and another 1g in10ml of olive oil (solvent 2), and each of the solutions was stored in a separate clean bottle for use in the solubility investigation.

Chloroform soxhlet extract of the powdered *W. laterita*

Figure 1: Cross-section of some bladder stones removed from vesicovaginal fistula patients.

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leaf (prepared by weighing 50g of the leaf into a round bottom flask containing 300 ml of chloroform, placed on the soxhlet apparatus, switched on, and allowed for 4hrs before being switched off, the flask was allowed to cool, and then concentrated to paste using a rotary evaporator. The paste was used to prepare aqueous solvent (solvent 7) and oil solvent (solvent 8). The solvents: 7 and 8 were then prepared by dissolving 1g of the *W.lateritia* leaf paste in 10 ml of water (solvent 7) and another 1 g in10 ml of olive oil (solvent 8), and each of the solutions was stored in a separate clean bottle for use in the solubility study.

Solubility analysis of the bladder stones

The solubility test method adopted in this study was described by [16]. A known weight of the stones was placed in cheesecloth tied with thread and then suspended in test tubes containing 10ml of the physiological solvent at an ambient temperature and allowed for 48 hours. The weight loss of the stones was evaluated after drying to a constant weight in an oven at 40°C and then subtracting the final weight from the initial weight.

The percentage dissolution was calculated using the following formula

% dissolution = (W initial – W final) X 100/W initial

Determination of uric acid

Principle: Uric acid undergoes oxidation and forms precipitates when treated with HNO_3. Procedure: Five drops of concentrated nitric acid were added into a test tube containing 1g of the ground bladder stones followed by heating in a water bath. The yellow color on the inner surface of the test tube indicates the presence of uric acid.

Determination of oxalate

Principle: In sulfuric acid solution, oxalate combines with hydrogen to form oxalic acid.

Potassium permanganate reacts with oxalate ions to produce carbon dioxide and water in an acidic condition as follows: permanganate ion is reduced to manganese solution, and the $5C_2O_4^{2-} + 2MnO_4^- + 16H + 10CO_2 + 8H_20 + 2Mn^{2+}$. The permanganate ion is intensely purple, whereas the manganese (II) ion is nearly colorless.

Procedure: Two (2) ml dilute sulphuric acid (2M H_2SO_4) were added to 1g of the ground sample stone in a test tube and then heat for1 min followed by the addition of two drops of potassium permanganate ($KMnO_4$). Discoloration and evolution of bubbles which confirmed the presence of oxalate were observed.

Determination of cystine

Principle: When cystine is boiled with 40% NaOH, some of the sulfur in its structure is converted to sodium sulfide (Na_2S). The Na_2S is detected by using sodium plumbate solution which causes the precipitation of PBS from an alkaline solution.

Procedure: Two (2) mls of the sample were boiled with 3 drops of 40% NaOH for 2 min. It was Cooled followed by the addition of 2 drops of sodium plumbate solution. A precipitate that confirmed the presence of sulfides was seen.

Determination of phosphate

Principle: Phosphate ions react with ammonium molybdate to produce a characteristic yellow the precipitate, ammonium phosphomolybdate.

Procedure: An amount, (0.1g) of the sample was dissolved in 1.5ml of concentrated nitric acid HNO_3. An equal volume (1.5ml) of ammonium molybdate solution was added. It was then heated to boiling. A yellow precipitate of ammonium phosphomolybdate confirmed the presence of phosphate.

ICP- OES (Inductively Coupled Plasma- Optical Emission Spectrometry) analysis

Principle: An aqueous sample is converted to aerosols via a nebulizer. The aerosols are transported to the inductively coupled plasma which is a high-temperature zone (8,000–10,000°C). The analytes are heated (excited) to different (atomic and/or ionic) states and produce characteristic optical emissions (lights). These emissions are separated based on their respective wavelengths and their intensities are measured (spectrometry). The intensities are proportional to the concentrations of analytes in the aqueous sample. The quantification is an external multipoint linear standardization by comparing the emission intensity of an unknown sample with that of a standard sample.

Procedure: Standard solutions were prepared and were confirmed against old working standard solutions and other independent primary standard solutions. As a routine daily operation, the ICP-OES instrument was started, brought to operation conditions, and allowed to stabilize. The sample introduction system was properly checked, and the wavelengths were tuned. The machine was standardized with the five working standard solutions (multi-point linear fitting). Samples were measured with standardization blanks, other kinds of blanks, drift control samples, and quality control samples. After measurement of a batch sample, the data were downloaded to an Excel spreadsheet and corrected in terms of standardization blanks, other relevant 2 blanks, drift correction, and dilution factor application. The results were normalized to the internal reference standard used.

GC-MS (gas chromatography-mass spectrometry) analysis

Principle: The GC (Gas chromatograph) works on the principle that a mixture will separate into individual substances when heated. The heated gases are carried through a column with an inert gas (such as helium). As the separated substances emerge from the column opening, they flow into the MS (Mass spectrometer).

Procedure: A quantity (1g) of the sample was injected into a port which was then heated up to 300°C where the sample

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was then volatilized. The samples were then separated based on their size and polarity as they flow through the column at an alternating temperature of about -20° to 320°. Sample components that are more volatile and smaller in size traveled through the column more quickly than others. The separated components flowed directly out of the column and into the mass spectrometer where it was ionized, filtered, and detected based on the number of filtered ions.

Fourier Transform Infrared (FTIR) analysis

Principle: The FTIR analysis uses infrared light to scan test samples and observe their chemical properties. The FTIR instrument sends infrared radiation of about 10,000 to 100 cm^{-1} through a sample, with some radiation absorbed and some passed through. The absorbed radiation is converted into rotational and/or vibration energy by the sample molecules. The resulting signal at the detector presents as a spectrum, typically from 4000 cm^{-1} to 400cm^{-1}, representing a molecular fingerprint of the sample. Each molecule or chemical structure will produce a unique spectral fingerprint.

Procedure: An amount (1g) of the sample was placed on the sample holder. The machine was switched on to analyze the sample.

Results

Tables 1-3.

Demographic characteristics showed that a higher incidence of VVF was between the ages of 2030; the highest level of education attained was a national certificate in education while their major occupation was petty trading.

Icp-ms study (Table 3) showed calcium, magnesium, potassium, sodium, manganese, iron, copper, aluminum, boron, chromium, nickel, and lead.

Table 4 showed uric acid, oxalate, cystine and phosphate in the bladder stones.

Table 5 showed that the bladder stones contained a varying degree of organic compounds: methylene chloride, dicloroacetaldehydes, cholesterol, Triacetone triperoxide (TATP), mecamylamine, Methenamine, etc Table 6.

Table 1: Demographic characteristics of the vesicovaginal fistula patients.

Age	n	%
20-30	-3	42.86
31-40	2	28.57
41-50	1	14.28
51-60	1	14.28
Total	7	100
Occupation		
Farmer	1	14.28
Petty trader	4	57.1
Secondary school teacher	1	14.28
Artisan	1	14.28
Total		100
Level of education		
Primary school	1	14.28
Secondary school	3	42.86
National certificate in education	2	28.57
University	0	100.00
No formal education	1	14.28
Total	7	100

Table 2: Effects of different solvents on the bladder stones.

S/No	Solvents	pH	Final weight	Initial weight	% variation
1	S1- Distilled water	6	0.12 ± 0.01	0.13 ± 0.005	7.75 ± 0.02^{c}
2	S2- Oil	6	0.16 ± 0.06	0.15 ± 0.04	$9.66 \pm 1.20^{*cd}$
3	S3- Whitfieldia lateritia leaf decoction	8	0.12 ± 0.02	0.13 ± 0.00	3.91 ± 0.50^{b}
4	S4- Aqueous solution of the Whitfieldia lateritia leaf soxhlet ethanol extract	7	0.13 ± 0.01	0.13 ± 0.02	1.56 ± 0.076^{a}
5	35-Olive oil solution of Whitfieldia lateritia leaf soxhlet ethanol extract	6	0.17 ± 0.00	0.15 ± 0.00	$11.26 \pm 1.50^{*d}$
6	S6- Occimum gratissimum (scent leave) decoction	6	0.15 ± 0.01	0.16 ± 0.00	3.75 ± 0.12^{b}
7	S7- Olive oil solution of Whitfieldia lateritia leaf chloroform extract	7	0.18±0.05	0.14 ± 0.26	$22.22 \pm 1.50^{*e}$
8	S8- Aqueous solution of the Whitfieldia lateritia leaf chloroform extract	8	0.14±0.016	0.15 ± 0.02	4.83 ± 1.80^{b}

Mean ± STD, n = 3. Values in the same column with similar superscripts are not significantly different (P>0.05). Starred (*) points gained weight.

Discussion

The metal and organic compositions of bladder stones removed from VVF patients at NOFIC were characterized. This is the first time an attempt is made to probe the metal and organic elements of the bladder stones removed from the VVF patients managed by the hospital.

The demographic patterns (Table 1) showed that a higher percentage (46.86) is between 20 to 30 years of age, their occupation varies from farming (14.28), petty trading (57.10), secondary school teaching (14.28), and artisan (14.28). The highest level of education attained was a national certificate in education while none has a university education. Poverty, illiteracy, poor access to maternal care services and lack of access to basic social services are among the factors that underlie VVF cases [15].

The in-vitro solubility tests of the bladder stones (Table 2) showed their variable solubility in different solvents. There was a significant ($p<0.05$) increase in the weights of the stones in the oil-based solvent plant extracts after 72 hours. This observation is consistent with the observed characteristic chemical components of the stone which will encourage attraction rather than chemical separation. However, the weights of the bladder stones were decreased in the aqueous-based solvent plant extracts, with the highest disease being

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Table 3: Metal concentration (PPM) of the bladder stones.

Parameter	Bladder stone 1	Bladder stone 2	Bladder stone 3	Bladder stone 4	Bladder stone 5	Bladder stone 6	Bladder stone 7
Ca	7.65 ± 0.05^a	1.48 ± 0.02^b	15.38 ± 1.10^c	7.65 ± 0.05^a	1.48 ± 0.02^b	15.38 ± 1.10^c	10.38 ± 1.11^c
Mg	4.67 ± 0.50^a	0.83 ± 0.50^b	5.80 ± 0.60^c	4.67 ± 0.50^a	0.83 ± 0.50^b	5.80 ± 0.60^c	2.70 ± 0.40^c
K	0.17 ± 0.01^a	1.06 ± 0.80^b	0.20 ± 0.05^b	0.17 ± 0.01^a	1.06 ± 0.80^b	0.20 ± 0.05^b	0.10 ± 0.05^b
Na	50.94 ± 1.50^a	74.39 ± 2.50^b	89.52 ± 1.50^c	50.94 ± 1.50^a	74.39 ± 2.50^b	89.52 ± 1.50^c	40.50 ± 1.50^c
Mn	1.80 ± 0.04^a	2.78 ± 0.50^b	2.79 ± 0.50^b	1.80 ± 0.04^a	2.78 ± 0.50^b	2.79 ± 0.50^b	2.79 ± 0.50^b
Fe	24.07 ± 1.20^a	18.36 ± 1.50^b	11.02 ±.50^c	24.07 ± 1.20^a	18.36 ± 1.50^b	11.02 ± 1.50^c	11.02 ± 1.50^c
Cu	1.03 ± 0.01^a	1.59 ± 0.01^b	2.16 ± 0.03^c	1.03 ± 0.01^a	1.59 ± 0.01^b	2.16 ± 0.03^c	2.16 ± 0.03^c
Zn	51.31 ± 1.51^a	28.83 ± 1.50^b	167.93 ± 5.00^c	51.31 ± 1.51^a	28.83 ± 1.50^b	167.93 ± 5.00^c	167.93 ±5.00^c
Al	7.98 ± 0.50^a	0.80 ± 0.01^b	BDL	0.42 ± 1.01^a	BDL	0.45 ± 0.10^a	BDL
B	1.08 ± 0.02^a	BDL	0.83 ± 0.45^b	1.08 ± 0.02^a	BDL	0.83 ± 0.45^b	BDL
Cd	BDL	BDL	BDL	0.36 ± 0.10^b	BDL	0.71 + 0.10^a	BDL
Co	0.20 ± 0.01^a	0.20 ± 0.01^a	0.12 ± 0.09^a	0.12 ± 0.09^a	BDL	0.12 ± 0.09^a	BDL
Cr	5.59 ± 0.50^a	2.86 ± 0.50^b	4.38 ± 0.50^c	2.50 ± 0.40^a	2.06 ± 0.20^b	1.34 ± 0.30^c	2.01 ± 0.10^b
Ni	BDL	BDL	BDL	0.20 ± 0.01	BDL	BDL	BDL
Pb	BDL	BDL	2.59 ± 0.50^a	0.59 ± 0.10^a	1.50 ± 0.20^a	0.70 ± 0.11^a	0.66 ± 0.02^b

Mean ± STD, n = 3. Values in the same column with similar superscripts are not significantly different (P>0.05).

Table 4: Qualitative Chemical Characterization of the bladder stones.

Sample/parameters	Uric acid	Oxalate	cystine	phosphate
Bladder stone 1	+	+	+	+
Bladder stone 2	-	-	-	+
Bladder stone 3	+	+	+	+
Bladder stone 4	+	+	+	+
Bladder stone 5	+	+	+	+
Bladder stone 6	+	+	+	+
Bladder stone 7	-	-	-	+

observed in the aqueous solution of soxhlet chloroform extract of *W. lateritia* leaf and *Ocimum gratissimum* leaf decoction. The bladder stone dissolution by the aqueous extract of *Ocimum gratissimum* leaf has been reported by Agarwal, et al. [17] who opined that *Ocimum gratissimum* leaf extract possessed significant dissolution and inhibition effect on calcium oxalate stones in vitro. This may be one of the mechanisms the *O. gratissimum* leaf decoction is used in traditional medicine as a body cleanser.

Our finding as shown in Table 3, implicated Ca, Mg, K, Na, Mn, Fe, Cu, Zn, Al, B, Cd, Co, Cr, Ni, and Pb in the bladder stones. Previous reports showed that while some elements have inhibitory effects, others promote stone formation. Trace elements can influence the external morphology of growing crystals and may increase or decrease the speed of the crystallization process [18]. Major and trace elements may contribute to the initiation of stone crystallization, and as a nucleus for the formation of the renal stone [19]. It has been demonstrated by some authors that metals such as magnesium, zinc, aluminum, iron, and copper may act as inhibitors of calcium oxalate growth at very low concentrations [20]. According to Meyer and Angino [21] copper inhibits the growth of calcium phosphate crystals but not calcium oxalate. Following previous studies on the total levels of elements in the bladder stones and the interactions of metals with promoters or inhibitors such as citrate, glycosaminoglycans, pyrophosphate, and Tamm–Horsfall protein [22], we suspect a potentiating effect of high concentration of the elements in diet vis-a-vis urinary supersaturation resulting from involuntary leakage of urine in VVF patients. It has been suggested that Magnesium could decrease calcium oxalate in the presence of its supraphysiologic concentration [23]. Also, Durak, et al. [22,24] demonstrated that a low level of magnesium in urine is a risk factor for lithogenesis while high levels of this element in urine reduce the concentration of oxalate available for calcium oxalate precipitation [25]. The role of iron in crystal formation is not clear. However, some authors argue that Fe3+ ions can establish stable chemical interactions with oxalate ions on the surface of calcium oxalate crystals, and can obstruct their development [20,26] but ferric ions are probably unable to act as an inhibitor in the presence of physiological concentrations of citrate due to the formation of highly stable complexes in solution without inhibitory activity [20,27]. Zinc has been shown to possess health benefits including reducing morbidity and mortality from diarrhea by protecting the immune system response[28]. But the data concerning its role in stone formation in the urinary tract are divergent [29]. Zinc has been reported in urinary stones by Amando [30] who reported a large amount of Zn in their study, and Zn can substitute calcium in stones crystals because of their similarity in charge and size and could promote calcium phosphate deposition in the medullar interstitium. Cadmium was not detected in many of the samples analyzed, and this is consistent with previous studies where Cd has been reported to be low even in patients who died of renal diseases [31]. Hofbauer, et al. [32]. Reported that Cd might have some inhibitory effect on calcium oxalate crystallization. Boron, just like Cd was found to be low or not detected in the bladder samples analyzed, and may as well have an inhibitory effect, since the work of Hunt, et al. [33]. Demonstrated low calcium oxalate in the excreted

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Table 5: Compounds identified from the GC-ms analysis of the bladder stone.

	Compounds	Chemical formula	Retention time	PEAK	AREA (%)
Sample 1					
1	**Triacetone triperoxde (TATP)**	**$C_9H_{18}O_6$**	**1.145**	**58**	**0.77**
2	3-Amino-2-oxazolidinone	$C_3H_6N_2O_2$	1.243	58	46.34
3	Butane, 2,2,3,3-tetramethyl	C_8H_{18}	1.36	57	6.08
4	Methenamine	$C_6H_{12}N_4$	1.919	140	3.57
5	Hydroxylamine, O-(3-methylbutyl)	$C_5H_{13}NO$	14.112	71	39.04
6	4-Aminosalicylic acid, 3TMS derivative	$C_{16}H_{31}NO_3Si$	18.366	528	1.41
7	Cholest-5-en-3-ol (3 beta)-, trifluoroacetate	$C_{29}H_{45}F_3O_2$	19.85	535	0.45
Sample 2					
1	2,5-Bis-(5-hexyl-[1,3,2]dioxaborinan-2-yloxy)-benzene	$C_{24}H_{40}B_2O_6$	0.661	446	1.99
2	Pentanethiol	$C_5H_{12}S$	1.208	63	94.28
3	Methylene chloride	CH_2Cl_2	1.302	86	2.66
4	Pentane, 2,2,3-trimethyl-	C_6H_{14}	1.703	57	1.86
5	Cyclobuta[de]naphthalene	$C_{11}H_8$	13.984	140	6.33
6	Methenamine	$C_6H_{12}N_4$	14.246	42	0.62
7	1,1-Difluoro-1-sila-5-thiacyclooctane	$C_6H_{12}F_2Si$	14.292	140	0.58
Sample 3					
1	2,5-Bis-(5-hexyl-[1,3,2]dioxaborinan-2-yloxy)-benzene	$C_{24}H_{40}B_2O_6$	0.638	446	1.4
2	2-(2-Furyl)-2,5-dimethyltetrahydrofuran	$C_{10}H_{14}O_2$	0.685	95	0.72
3	Hexanal	$C_6H_{12}O$	0.76	44	0.65
4	Ethylene oxide	C_2H_4O	0.848	44	0.5
5	Azetidine, 1-cholo-	C_3H_6ClN	1.133	42	1.95
6	Butanoic acid, 3-oxo-, 2-chloroethyl ester	$C_6H_9ClO_3$	1.203	43	46.72
7	Acetic acid, butoxyhdroxy-,butyl ester	$C_{10}H_{20}O_4$	1.302	41	33.4
8	Cyclobuta[de]naphthalene	$C_{11}H_8$	1.889	140	5.68
Sample 4					
1	Methyl 2-Hydroxyethyl Sulfoxide	$C_3H_8O_2S$	1.226	45	7.178
2	Methylene chloride	CH_2Cl_2	1.331	49	92.822
Sample 5					
1	Mercaptamine	C_2H_7NS	1.249	30	1.095
2	Propanone, 1,1-diethoxy-	$C_7H_{14}O_3$	1.331	43	79.789
3	Dichloroacetaldehyde	$C_2H_2Cl_2O$	18.145	49	6.183
4	Cyclooctasiloxane, hexadecamethyl-	$C_{16}H_{48}O_8Si_8$	21.905	355	2.664
5	Cyclodecasiloxane, eicosamethyl-	$C_{20}H_{60}O_{10}Si_{10}$	24.029	73	0.839
6	Cholesteryl Formate	$C_{28}H_{46}O_2$	34.278	368	1.913
7	Cholesterol	$C_{27}H_{46}O$	36.601	386	7.517
Sample 6					
1	dl-Allo-cystathionine	$C_7H_{14}N_2O_4S$	1.243	47	11.737
2	Methylene chloride	CH_2Cl_2	1.319	49	84.212
3	Cholesterol	$C_{27}H_{46}O$	36.56	43	4.051
Sample 7					
1	Carbamic acid, monoammonium salt	$CH_6N_2O_2$	1.174	44	2.426
2	dl-Allo-cystathionine	$C_7H_{14}N_2O_4S$	1.255	47	25.209
3	Dichloroacetaldehyde	$C_2H_2Cl_2O$	1.366	49	49.199
4	Cholest-5-en-3-ol (3β)-, acetate	$C_{29}H_{48}O_2$	33.155	43	2.596
5	Cholesta-3,5-diene	$C_{27}H_{44}$	33.987	43	4.452
6	Cholest-5-ene, 3-(1-oxobuthoxy)-	$C_{31}H_{52}O_2$	34.302	43	16.117

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Table 6: Functional groups identified from the FTIR of the bladder stones.

	Wavelength	Functional group
Bladder stone 1	3850-3641	O-H Stretching
	3086	Aromatic C-H stretching
	2978	Aliphatic C-H stretching
	1681	C=O or C=N stretching
	1080	C-O stretching
Bladder stone 2	3850-3618	OH stretching
	3078)	Aromatic C-H stretching
	2947	Aliphatic C-H stretching
	2345	C ≡ N or C ≡ C
	1681	C=N or C=O
	1512	C=C
	1057	C-O
Bladder stone 3	3850-3580	O-H stretching
	3078	Aromatic C-H stretching
	2962 & 2885	Aliphatic C-H
	2337	C ≡ N or C ≡ C
	1681	C=N or C=O
	1072	C-O
Bladder stone S4	3054	Aromatic C-H stretching
	2987-2918	Aliphatic C-H stretching
	2305-2025	C ≡ C or C ≡ N stretching
	1422	C=C stretching
	1265	C-O stretching
	730-896	out of plane bending stretching
Bladder stone S5	3054	Aromatic C-H stretching
	2987-2922	Aliphatic C-H stretching
	2305-2158	C ≡ C or C ≡ N stretching
	1422	C=C stretching
	1265	C-O stretching
	730-896	out of plane bending stretching
Bladder stone S6	3054	Aromatic C-H stretching
	2987	Aliphatic C-H stretching
	2305	C ≡ C or C ≡ N stretching
	1422	C=C stretching
	1263	C-O stretching
	730-896	out of plane bending stretching
Bladder stone S7	3054	Aromatic C-H stretching
	2987-2918	Aliphatic C-H stretching
	2305-2025	C ≡ C or C ≡ N stretching
	1422	C=C stretching
	1265	C-O stretching
	730-896	out of plane bending stretching

The FTIR revealed C-O stretching, Aromatic C-H stretching, C-O stretching, O-H stretching, aromatic Hstretching, C ≡ N stretching, etc.

urine of postmenopausal women as a metabolic response to dietary boron supplementation. Low boron was observed in our study. This is consistent with what had been observed in patients with cystine stones [34]. The role of leadership in bladder stone formation is unknown but some authors have found the correlation between lead level in lithogenesis and lead in stones and urine, and may lead to the conclusion that it may play some role in the process of crystallization in the urinary tract [35]. The inhibitory activity of Co, Ni, Pb, Sn, and Zn on the process of stone formation had been reported [32]. Na/k ratio was generally high in our study. The previous study has shown that individuals with a high urinary Na to K (Na/K) ratio, caused by high Na and/or low K excretion, are at a higher risk of urinary stone disease [36]. Generally, Mineral elements (e.g. Zn, Fe, and Ca) found in this study might be potential agents of bladder stone formation.

This study showed that uric acid, oxalate, cystine, and phosphate were present in the bladder stones (Table 4). This observation is in tandem with the previous reports [37]. Oxalate forms complexes with metals, which can crystallize and be deposited in the bladder over time. Robertson [38] posits that the main factor that leads to the formation of bladder stones in children is a nutritionally poor diet that is low in animal protein, calcium, and phosphate, but high in cereal and is acidogenic; with the consequential formation of urine with a relatively high content of ammonium and urate ions which could lead to the formation of ammonium acid urate crystals and stones. The stone problem is compounded by poor oral intake of water, excessive fluid losses through sweating from the skin, and a high intake of local vegetables rich in oxalate [38]. Furthermore, VVF patients are usually low-income earners, and rural dwellers, with minimal education, and these social factors may also underlie the formation of bladder stones among these vulnerable groups of women [2]. The uric acid, oxalate, cystine, and phosphate reported in this study might have been a driving agent in the formation of bladder stones among VVF patients.

The GC-ms results (Table 5) as indicated by the peaks in the chromatogram (Figure 2) showed the following compounds: methyl 2-Hydroxyethyl sulfoxide; methylene chloride; mercaptamine; 1,1diethoxy,dichloroactealdehyde; hexadecamethyl; Cyclopentasiloxane; eicosamthyl-; monoammonium salt, dl-Allo-Cystathionine, dichloroacetaldehyde, cholest-5-ene,3-(1oxobuthoxy)-); 2,5-Bis-(5-hexyl-[1,3,2]dioxaborinan-2-yloxy)-benzene; 2-(2-Furyl)-2,5dimethyltetrahydrofuran; Hexanal; Methenamine; 1,1-Difluoro-1-sila-5-thiacyclooctane; Butanoic acid, 3oxo-, 2-chloroethyl ester; Triacetone triperoxide; 4-Aminosalicylic acid, 3-Trimethylsilyl (3TMS) derivative; Pentanethiol; and 2,5-Bis-(5-hexyl-[1,3,2]dioxaborinan-2-yloxy)-benzene. Most of these compounds identified suggested possible abuse of drugs (synthetic or herbal medics) as most of the compounds are either drugs or drug metabolites, for example, 3-Amino-2- Oxazolidinone (a metabolic product of furazolidone used as an antiprotozoal, feed additive for poultry, cattle, fish, etc) [39,40]. Cyclodecasiloxane, one of the active compounds in Anacardium occidentale commonly used in herbal medics [41,42]. Methenamine is used for the treatment of urinary tract infections; 4Aminosalicylicacid, 3TMS derivative (antitubercular agent), and pentanethiol (thiol derivatives have different medical applications e.g. 6-Mercaptopurine (anticancer), Captopril (antihypertensive)) [43]. Steroid derivatives that were detected might be products of either birth pills or antimicrobial drugs since cholesterol analogs with non-degradable side chains form part of a novel class of antimycobacterial agents as demonstrated by chlest-4-en-3-one which is known to inhibit the growth of mycobacterium [44]. This is just adding to our earlier opinion that the abuses of drugs by the patients might have contributed to either causation or acceleration of the bladder stone formation since their demographic data (Table 1) showed that they are low-income earners who might not have access to quality diet, drinking water, and quality education, and are likely to patronize street drugs including traditional medics at the onset of clinical symptoms of VVF disease. Self-medication is common among

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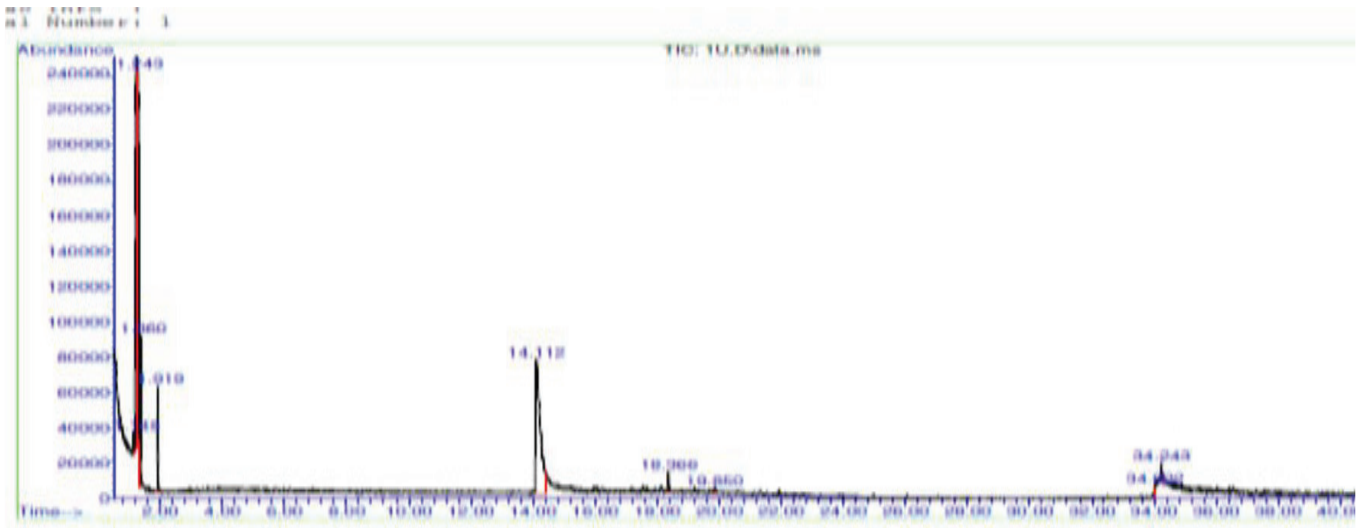
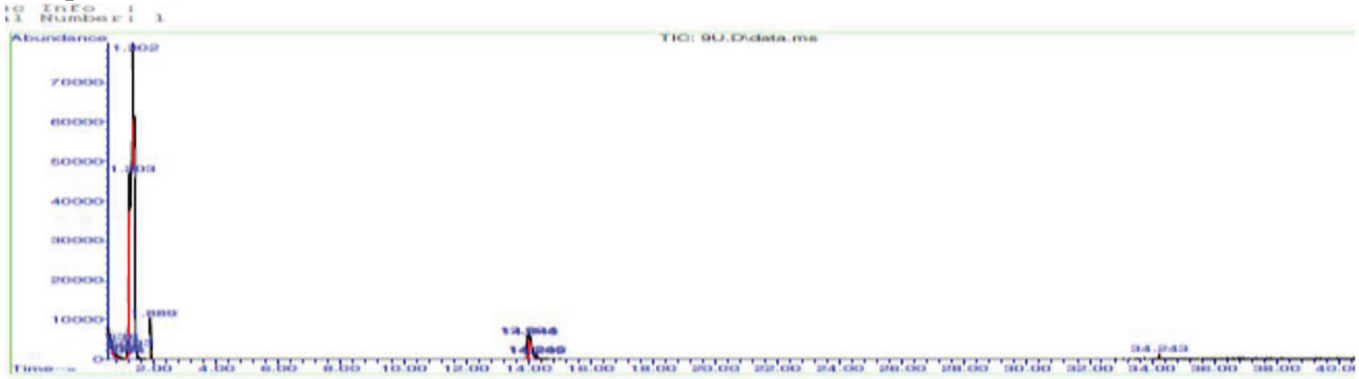


Sample 1

Sample 2



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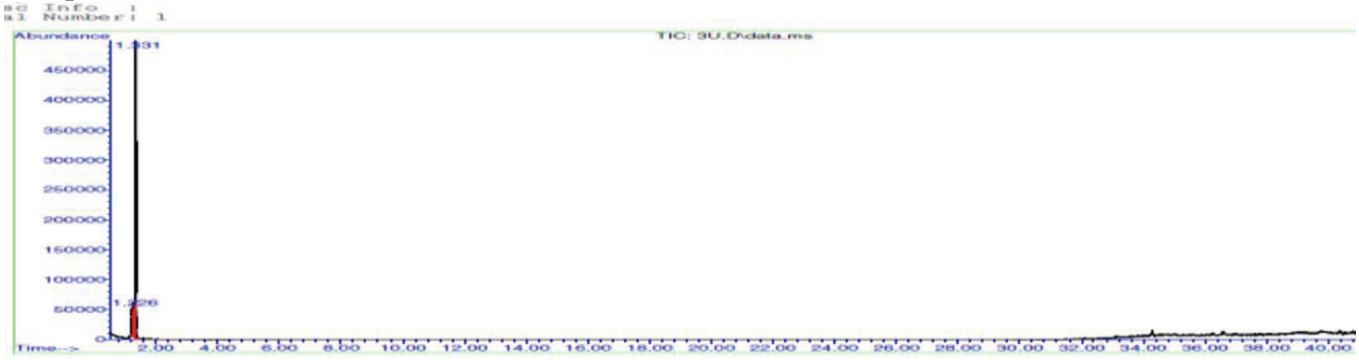

Sample 4

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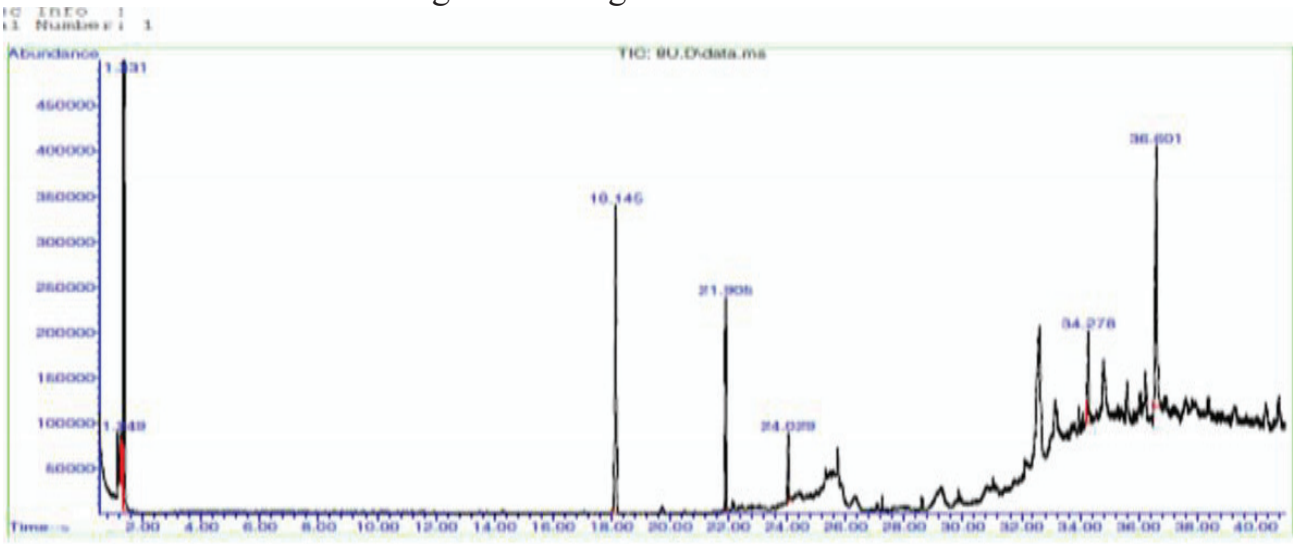
Continuation of the chromatogram of the gc-ms of bladder stones



Sample 5

Sample 6

Sample 7

Figure 2: The chromatogram of gc-ms analysis of the bladder stones (samples 1-7)

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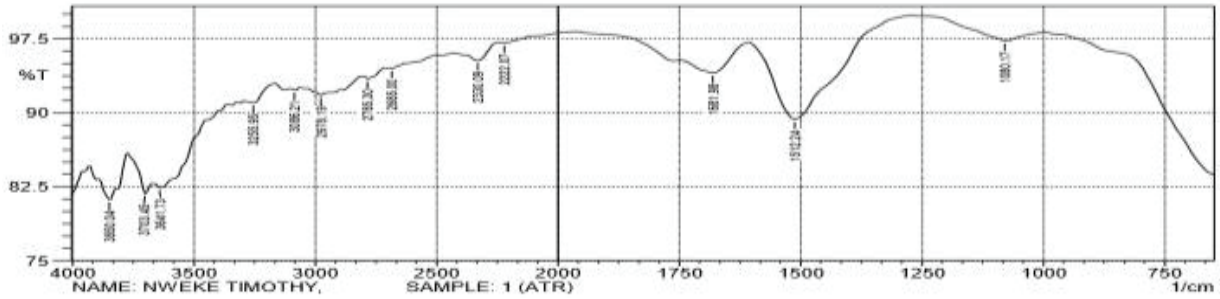
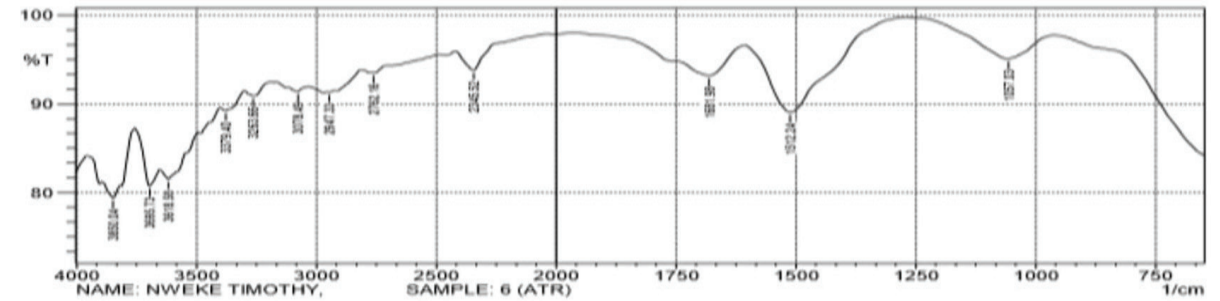
women, especially those of younger age (mostly students), who have lower socioeconomic status and chronic ailment, and patronize over-the-counter drugs (OTDs) that are freely displayed in unauthorized places in Nigeria [45]. Hundred percent (100%) of the patients (Table 1) have no university education, 57 % are petty traders and of course, many of them are below 30 years (table 1). The use of un-prescribed products by the patients might lead to metabolic abnormalities that facilitated the formation of bladder stones. The loop diuretics; carbonic anhydrase inhibitors; and laxatives can induce metabolic calculi when abused and occurs the drug's metabolites crystallize and become the primary component of the stones. According to Brien, et al. [46] magnesium trisilicate, ciprofloxacin, sulfa medications, triamterene, indinavir, and ephedrine alone or in combination with guaifenesin are medications that can induce calculi via this process. Eliminating or reducing the abuse of synthetic drugs or herbal medics may attenuate stone activity.

The FTIR (Table 5) revealed C-O stretching, Aromatic C-H stretching, C-O stretching, O-H stretching, aromatic H-stretching, C≡N stretching, etc as indicated by the FTIR chromatogram (Figure 3) that confirmed the chemical compounds identified. Similar chemical groups had been reported by Kanchana, et al. [47] Bladder stone composition



Sample 1



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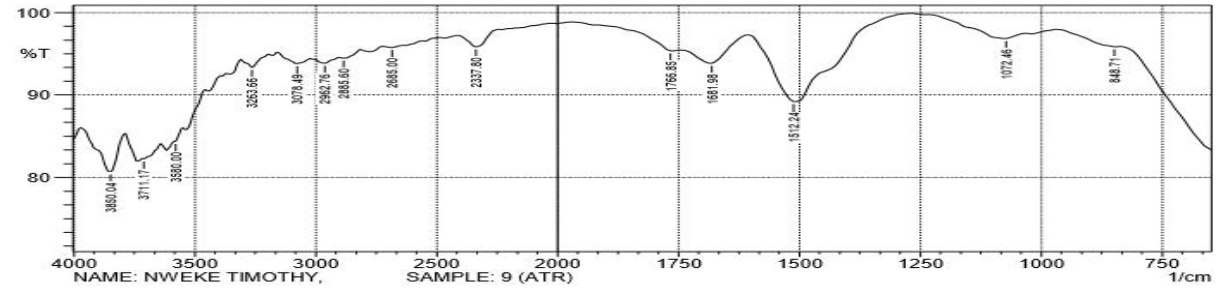
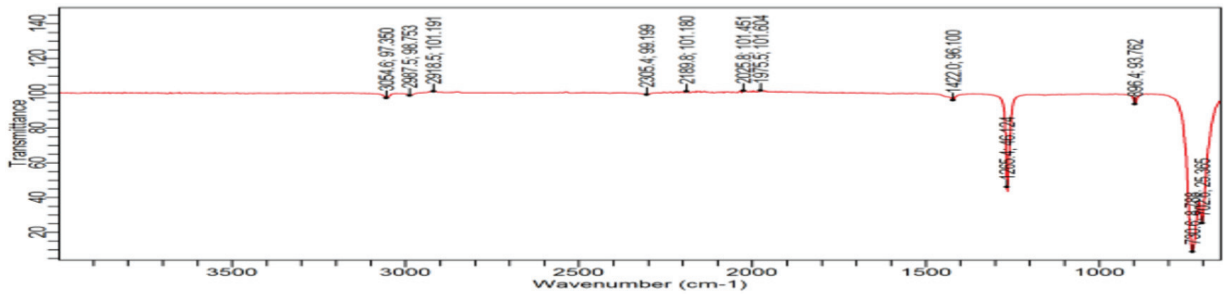


Sample 3



Sample 4

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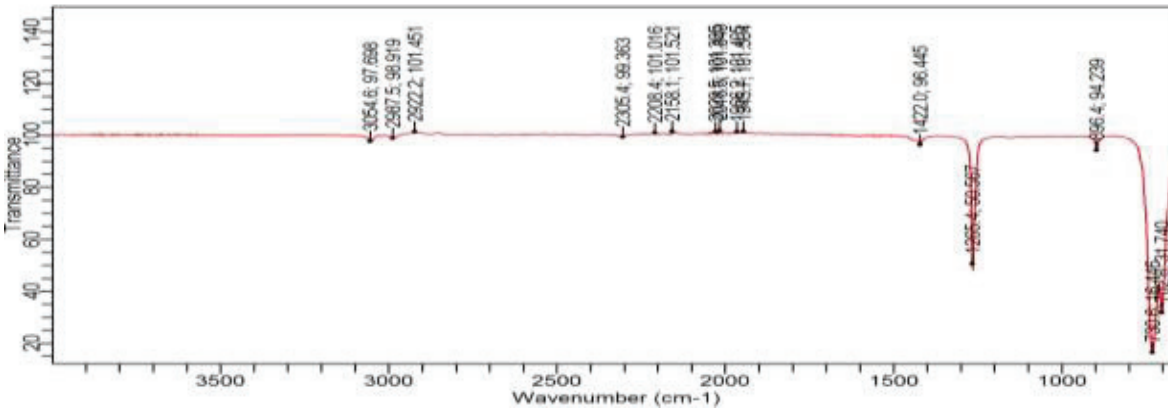
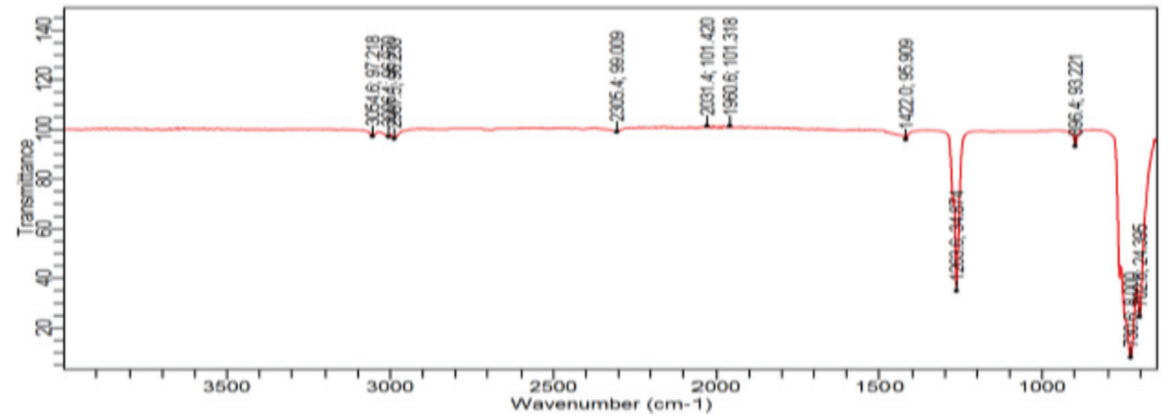
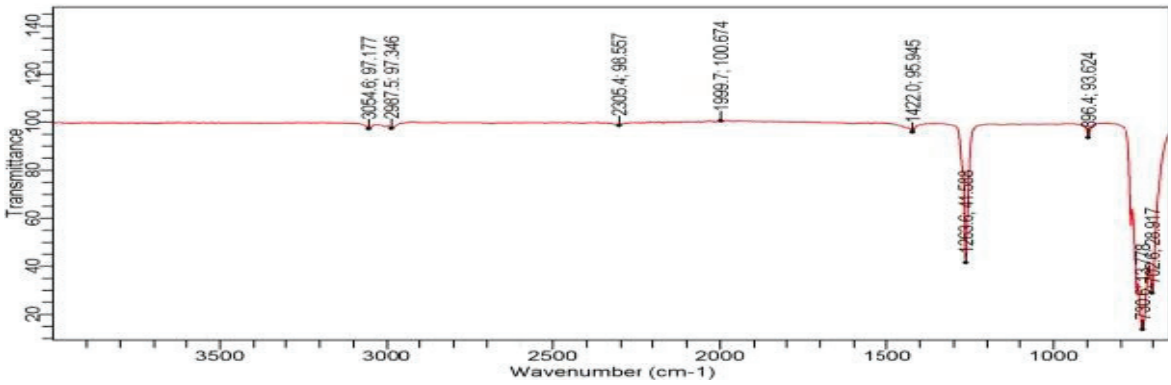
Continuation of the chromatogram of FTIR of the bladder stones



Samples 5



Sample 6



Sample 7

Figure 3: The chromatogram of FTIR of the bladder stones.

is affected by dietary adaptations, geography, socioeconomic conditions, urinary tract anatomical defects, infections, and metabolic disorders. Defining stone composition is important for determining a treatment plan, understanding aetiology, and preventing recurrence [9]. FTIR could possess good sensitivity in bladder stone profiling that may be critical in clear-cut identification of the elements making up the stones.

The development of any potential drug infusions with the capacity to dissolve the stones in-vivo, and to be applied as a treatment regime for bladder stones, starts with the understanding of the structure and functional properties of the bladder stones. Thus, the next phase of the research will involve exploring the functional element/groups identified to design infusions that may be more efficient in the dissolution of the stones in-vivo than the solvents (plant extracts) already tested in the dissolution of the stones to prevent/manage bladder stone problems which may remove new dimension to the timing and extent of the surgery in the VVF patients.

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