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## Potential anticancer, antiviral and antimicrobial effect of Red Sea soft coral

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**Abstract**

*SarcophytonConvolutum*extract (S) is rich source of bioactive secondary metabolite. In this article we report identification of major components and study antimicrobial, anticancer and antiviral activities of non-polar *SarcophytonConvolutum*extract.Results demonstrated that *S. Convolutum*extract (S) has strong bactericidal effect against *P. aeruginosa* ATCC 15442recordingMIC value about 0.05µg/mL.*S. Convolutum*extract (S) showed cytotoxicity against hepatocellular carcinoma cell line (HepG2), human colorectal adenocarcinoma (CaCo2), breast cancer cell line (MCF-7), and pulmonary adenocarcinoma (A549) and recorded $IC_{50}$ of 102.73, 100.62, 86.68 and 81.64 while antiviral activity towards HSV-1 and HAV virus at the maximum nontoxic concentration was 32.69% and 11.53%, respectively. GCMS analysis of *S. Convolutum*extract (S) showed about 25 compounds about 45.31% of extract is sesquiterpene, 47.53 % fatty acid derivatives 3.13% steroids and 2.2% is retinal diterpene.Our in vitro study indicates that sesquiterpene rich softcoral*S. Convolutum*extract (S) is a promising anticancer and antimicrobial agent but weak antiviral agent.

**Keywords:** *Sarcophyton Convolutum;* sesquiterpene; anticancer; antimicrobial; antiviral.

## 1. Introduction

Cancer is one of the most fatal diseases worldwide. According recent studies, cancer may exceed cardiovascular disease (CVD) as a main reason of premature death in most countries all over the world. For every 10 persons who die prematurely 3 die of cancer [1,2].

Synthetic antitumor drugs are being used but not recommended because some of them have non-selective mechanism and prolonged usage causes bone marrow depression, alopecia and nephrotoxicity, other which has high selective mechanism on cancer cells has very low efficacy as anti-tumor agent and prolonged use of it cause uterine and endometrial tumors. So we need new anti-tumor agent with high efficacy and low side effects[1,2].Herpes simplex virus (HSV) is an enveloped double stranded DNA virus whereas Hepatitis A virus (HAV) is non-enveloped, single-stranded RNA virus. For HAV, 1.4 million cases are being recorded every year worldwide. the danger of HAV virus is represented in its spread and its complication like liver cirrhosis and hepatocellular carcinoma [3,4]. HSV include two subtype, HSV-1 which causes oral herpes and encephalitis and HSV-2 which responsible for genital herpes. Effective anti-herpes virus drugs are being used like acyclovir, valacyclovir and other drugs that destroy virus DNA but due to antivirus drug resistance it is urgent to develop novel anti-virus drugs[5]. Marine environment is a rich source of valuable natural products and provides a broad panel of diverse chemical structures with promising bioactivities

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useful as therapeutic agents[6]. Red Sea coral reef is one of the most promising areas for exploring biologically active secondary metabolites; the highest salinity (about 39.79- 41.52) and warmest temperature (about 20˚ in winter and 27.49˚ in summer) increase its biodiversity[7,8]. Sarcophyton species are one of the most common species in red sea coral reef. Lots and diverse secondary metabolites including diterpenes, steroids and sesquiterpenes were isolated and spectrally characterized from these species. Lots of these isolated compounds compounds such as sarcoconvolutum A–G have biological activities, i.e., cytotoxic, anti-inflammatory and antimicrobial activities[9–16]. Sesquiterpene is class of terpenes that has significant interest due to its biological activity. Thousands of different sesquiterpene compounds that have been identified, these compounds differ in the layering of their functional groups and substitution but having the same C-15 carbon skeleton[17]. Our present study disclosed charachterization of major compounds using GC/MS analysis of Red sea soft coral, *sarcophytonconvolutum*and evaluation of the cytotoxic effect of *sarcophytonconvolutum*extract (S) towards four human cancer cell lines; hepatocellular carcinoma cell line (HepG2), human colorectal adenocarcinoma (CaCo2), breast cancer cell line (MCF-7), and pulmonary adenocarcinoma (A549) also antiviral activity of the extract towards herpes simplex virus (HSV-1) and hepatitis A virus (HAV). The antimicrobial activity of *S. convolutum*extract (S) was also determined.

## 2. Materials and Methods

### *2.1. Sample collection*

The soft coral, *S. convolutm*, was kindly collected and identified by Dr.Elsayedabd-Elaziz researcher at the National Institute of Oceanography and Fisheries (NIOF) in November 2020, from the Red Sea at a depth of 4-5 m at the front of Hurghada marine station of National Institute of Oceanography and Fisheries, Hurghada, Egypt. The sample was reserved in -20˚ until transferred to biotechnology laboratory for extraction.

### *2.2. Extraction and isolation*

Frozen marine organism was crushed using chopper to small pieces then extracted at room temperature with a mixture of ($CH_2Cl_2$/MeOH, 50/50) until complete extraction. After filtration, the extract was concentrated under reduced pressure at 40 ºC. The residue (40.0 g) was subjected to silica gel column eluted with 20% (ethyl acetate:hexane; 1:4) Extract (*S*) was evaporated to dryness, where non-polar yellow residues were obtained. This residue was then subjected to biological studies and also analysed by GC/MS technique for identification of its major components.

### *2.3. Determination of antibacterial activity*

Agar well diffusion method was used to investigate the *in vitro* qualitative antibacterial activity screening of (S) extract against five pathogenic bacterial strains, Gram-negative pathogenic bacteria including *Escherichia coli* ATCC 8739, *P. aeruginosa* ATCC 15442 and *Klebsiella pneumoniae* ATCC 13883while the tested Gram-positive strains were *Enterococcus faecalis* ATCC 29212, and *Staphylococcusaureus* ATCC 25923. The minimum inhibitory concentration(MIC) as the quantitative screening was investigated performing a broth dilution assay using a bacterial suspension of 0.5 McFarland density obtained from 24 -hour cultures were incubated at 37 °C. Uniform microbial lawns were prepared using sterilized swabs after dispensing 500 µL of already standardized culture. Each agar well loaded with 100 µL (S) extract dissolved in DMSO (50000 – 0.005 µg/mL) final concentrations were carefully placed on the microbial lawns while DMSO was used as a control. Zones of inhibitions (ZOI) were recorded in millimeters. MICs were calculated using a broth dilution assay by applying further lower concentrations of bioinspired *S. Con*. The lowest one at which no visible growth of the bacteria was observed considered as MIC[18].

### *2.4. Determination of anticancer activity*

The cytotoxic effect of *sarcophytonconvolutum*extract (S)towards four human cancer cell lines; hepatocellular carcinoma (HepG2), human colorectal adenocarcinoma (CaCo2), breast cancer cell line (MCF-7), and pulmonary adenocarcinoma (A549) was evaluated using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells were cultured in 96-well microplates then incubated for 24 h at 37 °C and 5% $CO_2$ in order to develop monolayer sheet. The growth medium was then decanted from all wells and the monolayer sheet was washed twice with washing media. The working solution of (S) was prepared freshly with different

concentrations of (S)extract (31.25- to 1000 µg/mL). A control experiment was carried out with solvent only (DMSO) without sample. Incubation of plates for 3 days then MTT is added then incubated for 1-5 h to permit the formation of formazan after that, DMSO is added and absorbance was measured at 560 nm. $IC_{50}$ values is determined [19–22].

***2.5. Determination of antiviral activity Determination of the cytotoxicity of SarcophytonConvolutum extract (S)on Vero cells***

Different concentration of *sarcophytonconvolutum* extract (S); (31.25, 62.5, 125, 250, 500 and 1000 µg/mL) were prepared in order to evaluate their cytotoxicity on African green monkey cell line (Vero cells; ATCC CCL-81) using MTT method. The maximum Non Toxic Concentration (MNTC); the concentration which didn't cause toxicity towards Vero cell was determined. Also cytotoxicity % was calculated by equation [(A-B)/Ax100]; A and B are the absorbance of control and treated cells, respectively. The $CC_{50}$value (the concentration that caused 50% toxicity) was evaluated [23].

***2.6. Cell line and viruses***

The used cell line was hepatocellular carcinoma cell line (HepG2), human colorectal adenocarcinoma (CaCo2), breast cancer cell line (MCF-7), pulmonary adenocarcinoma (A549), African green monkey (Vero; ATCC: CCL-81) and the viruses were herpes simplex virus (HSV-1) and hepatitis A virus (HAV) were obtained from Faculty of medicine for girls, Al-Azhar University, Cairo, Egypt**.**

***2.7. Antiviral assay***

The antiviral activity was carried out by MTT assay as previously described [22,23]. Briefly,Vero cell culture (10,000 cells/200 µL of media) were dispensed in each well of 96-well plate then incubated over night to permit the cells to attach to the wells. A mix of virus / sample was then prepared and incubated for 1 h, then shaken and finally incubated for 24 h. after incubation MTT is added in order to permit formation of Formozan. DMSO (about 200 µL) is added and the optical density was determined at 560 nm and the background was subtracted at 620 nm. $IC_{50}$ and$CC_{50}$ were calculated. The antiviral activity was evaluated according to the equation:

Antiviral activity (%) = $(A - B)/(C - B)\ x100$

Where A, B and C are the absorbances of sample, virus and cell control

***2.8. GCMS analysis***

GC-MS analysis of non-polar volatile extract was performed on Agilent 5977C single quadrupole GC/MS instrument (National Institute of Oceanography and Fishers).

**3. Results**

***3.1. Antibacterial activity***

Here, the antibacterial activity of (S) extract was evaluated against some pathogenic strains. Results obtained from the experiment revile that *S. Con*extract has antibacterial activity against *P. aeruginosa* ATCC 15442 that increases with an increase in its concentration. On the other hand, *S. Con*extract has no antibacterial activity against *Escherichia coli* ATCC 8739, *Klebsiella pneumoniae* ATCC 13883, *Enterococcus faecalis* ATCC 29212, and *Staphylococcusaureus* ATCC 25923 (Figure**1**), meanwhile, no ZOI was observed around the control. These results indicate that (S) extract showed a strong bactericidal effect against *P. aeruginosa* ATCC 15442 proved to be susceptible to the tested (S) extract.Following the qualitative screening, the activity of (S) extract further revealed using the quantitative assay for establishing the MIC value. This assay showed that (S) extract generally inhibits the growth of *P. aeruginosa* ATCC 15442 cells from the highest tested concentrations of 50000 µg/mL to 0.05 µg/mL, as demonstrated in figure **2**. The MIC value of (S) extract observed to be 0.05µg/mL for *P. aeruginosa* ATCC 15442.

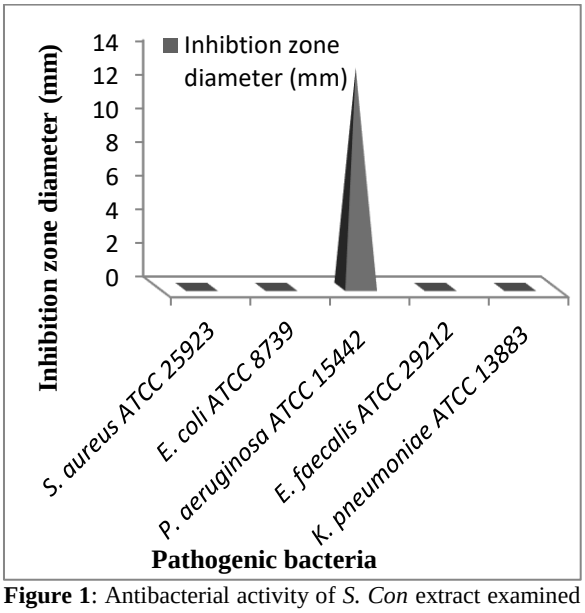


**Figure 1**: Antibacterial activity of *S. Con* extract examined

against some pathogenic bacteria including *Escherichia coli*ATCC 8739, *P. aeruginosa*ATCC 15442, *Klebsiella pneumonia* ATCC 13883, *Enterococcus faecalis* ATCC 29212, and *Staphylococcus aureus* ATCC 25923 using the agar diffusion method.

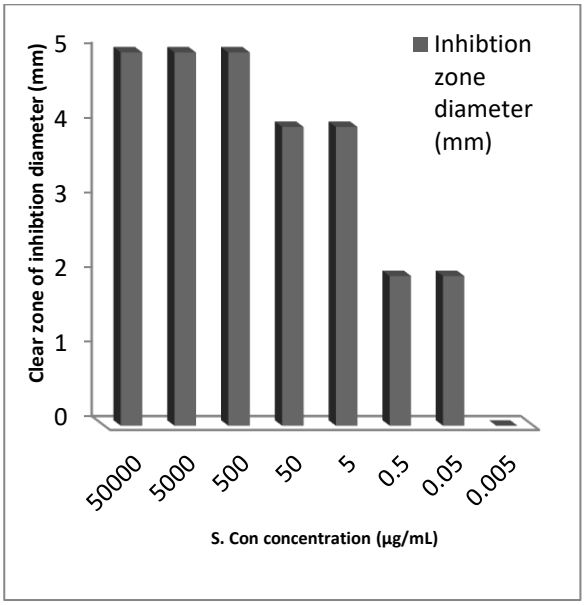


**Figure 2**: Antibacterial MIC value for *P. aeruginosa* ATCC 15442 at 24 h of incubation (0.05 µg/mL).

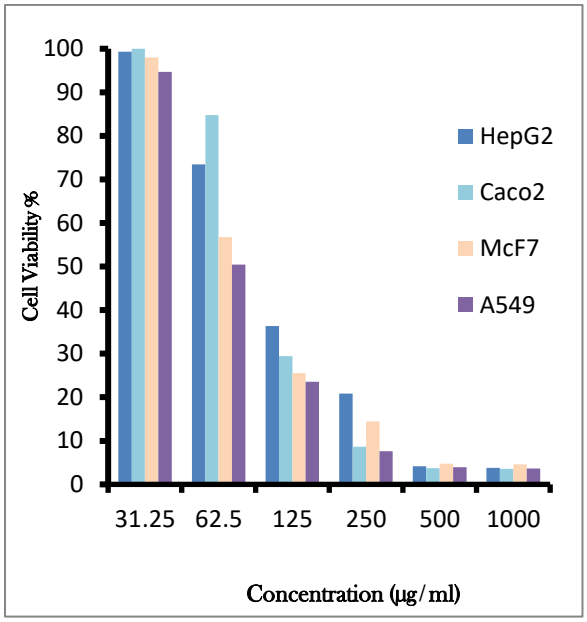


**Figure 3:** Cytotoxicity activity of *S.con* extract against hepatocellular carcinoma cell line (HepG2), human colorectal adenocarcinoma (CaCo2), breast cancer cell line (MCF-7), and pulmonary adenocarcinoma (A549) by the MTT assay. Data are expressed as means (n=3) ± standard deviation.

### 3.2. Anticancer activity

Figure (3) illustrates the cytotoxic effect of *S. convolutum*extract (*s.con*) towards four human cancer cell lines; hepatocellular carcinoma cell line (HepG2), human colorectal adenocarcinoma (CaCo2), breast cancer cell line (MCF-7), and pulmonary adenocarcinoma (A549).

The results revealed that the *S.con* extract, at concentration ranging from 31.25- 1000 µg/mL have markedly effect in reduction of cell viability toward all tested human cancer cell lines. Cell viabilities of the tested cancer cell lines at the maximum concentration of the extract (1000 µg/mL) tested was 3.8%, 3.5%, 4.6% and 3.6% for HepG2, CaCo2, Mcf-7 and A549, respectively.

**Table 1:** $IC_{50}$ of *S.Con* extract against hepatocellular carcinoma cell line (HepG2), human colorectal adenocarcinoma (CaCo2), breast cancer cell line (MCF-7), and pulmonary adenocarcinoma (A549)

| Cell line | $IC_{50}$ |
|---|---|
| HepG2 | 102.73 |
| CaCo2 | 100.62 |
| McF-7 | 86.68 |
| A549 | 81.64 |

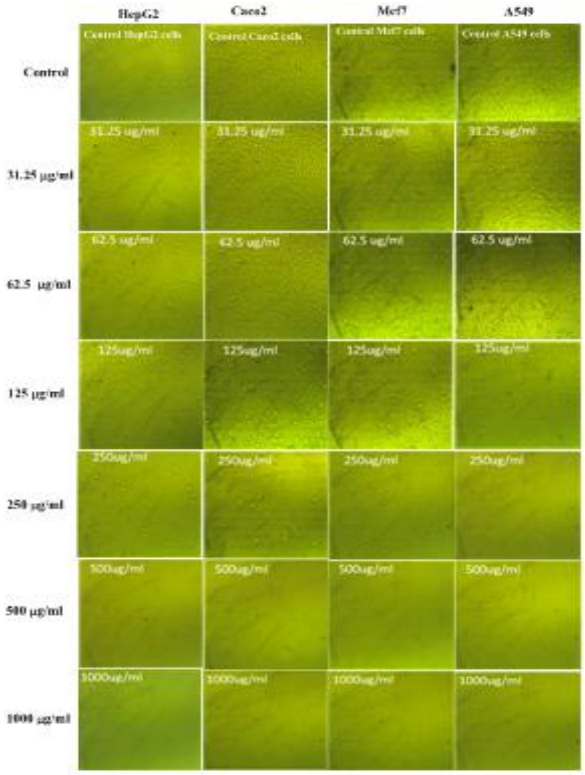


**Figure 4:** cytotoxic effect and variation in morphological characteristics of human hepatocellular carcinoma cell line (HepG2), human colorectal adenocarcinoma (CaCo2), breast cancer cell line (MCF-7), and pulmonary adenocarcinoma (A549) treated with different concentrations (31.25-1000 µg/mL) of non-polar extract of *S.con*species compared with untreated cell lines (control).

### 3.3. Antiviral activity

In our study examination of the antiviral activity of 20% (ethyl acetate/hexane) Extract (*S*) against HSV-1 and HAV virus was determined using MTT method in which Extract (*S*) exhibited weak antiviral activity. The 50% cytotoxic concentration ($CC_{50}$) of the extract on Vero cells was 121.163 µg/mL and the maximum non-toxic concentration was 31.25 µg/mL (Figure 5). The antiviral activity of the extract at the maximum nontoxic concentration was 32.69% and 11.53% against HSV-1 and HAV virus, respectively.

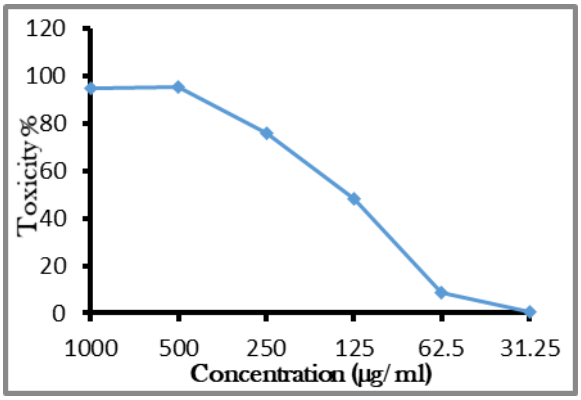


**Figure5**: Cytotoxicity of *S.con* extract on Vero cell of different concentration

### 3.4. GC-MS analysis

qualitative and quantitative GCMS of major compositions of *S.con* extract (S) were analyzed (Figure 6, 7 and table 2) revealed that extract is rich withSesquiterpenoids; total Sesquiterpenoid accounts of 45.33% of whole extract in addition to Fatty acid and fatty acid derivatives which accounts about 47.53% of whole extract.as mentioned in table 2 the most abundant constituents of *S.con* extract (S) were found to be aromandendrene**(2)**about (5.51%), (+)-ledene**(3)**about (5.27%), (+)-viridiflorol**(8)**about (13.77%), methyl palmitate **(15)**about(5.51%), Palmitic acid **(17)**about(13.56%), myristylmyristate**(21)**about(5.06%)and Palmityl palmitate (23) about (13.01%).

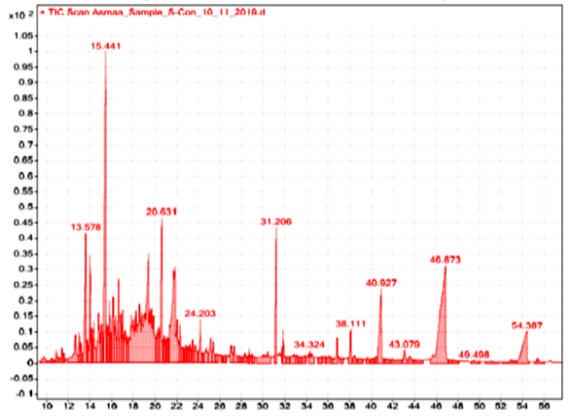


**Figure 6:** GC chromatogram of *S. convolutum*

**Table 2:** Chemical constituents of 20% (ethyl acetate/hexane) *S.convolutum*extract (S)

| *Compound name* | *RT* | *Area%* | *class* | *Mol. For* | *Mol.Wt* |
|---|---|---|---|---|---|
| γ-gurjunene (1) | 12.63 | 2.9 | Sesquiterpenoid | $C_{15}H_{24}$ | 204 |
| aromandendrene (2) | 13.00 | 5.51 | Sesquiterpenoid | $C_{15}H_{24}$ | 204 |
| (+)-ledene (3) | 13.55 | 5.27 | Sesquiterpenoid | $C_{15}H_{24}$ | 204 |
| L-calamenene (4) | 13.99 | 3.78 | Sesquiterpenoid | $C_{15}H_{22}$ | 202 |
| α-ylangene (5) | 14.14 | 0.87 | Sesquiterpenoid | $C_{15}H_{24}$ | 204 |
| α-calacorene (6) | 14.34 | 1.67 | Sesquiterpenoid | $C_{15}H_{20}$ | 200 |

| | | | | | |
|---|---|---|---|---|---|
| nootkaton-11,12-epoxide (7) | 14.75 | 3.42 | Sesquiterpenoid | $C_{15}H_{22}O_2$ | 234 |
| (+)-viridiflorol (8) | 15.39 | 13.77 | Sesquiterpenoid | $C_{15}H_{26}O$ | 222 |
| cubenol (9) | 15.79 | 1.7 | Sesquiterpenoid | $C_{15}H_{26}O$ | 222 |
| 7-isopropyl-1,4-dimethyl-azulene (10) | 16.62 | 3.06 | Sesquiterpenoid | $C_{15}H_{18}$ | 198 |
| corymbolone (14) | 20.34 | 1.26 | Sesquiterpenoid | $C_{15}H_{24}O_2$ | 236 |
| 6-(1-hydroxymethylvinyl)-4,8a-dimethyl-3,5,6,7,8,8a-hexahydro-1H-naphthalen-2-one (16) | 20.84 | 2.12 | Sesquiterpenoid | $C_{15}H_{22}O_2$ | 234 |
| ***Total Sesquiterpenoid = 45.33%*** | | | | | |
| retinal (11) | 16.83 | 2.61 | diterpene | $C_{20}H_{28}O$ | 284 |
| ***TotalDiterpene* = 2.61** | | | | | |
| cholesta-4,6-dien-3-ol (20) | 38.09 | 1.4 | Steroid | $C_{27}H_{44}O$ | 384 |
| usodeoxycholic acid (22) | 43.54 | 1.73 | Steroid der. | $C_{24}H_{40}O_4$ | 392 |
| ***Total Steroid = 3.13*** | | | | | |
| methyl myristate (12) | 17.00 | 1.73 | Fatty ester | $C_{15}H_{30}O_2$ | 242 |
| 2-methylhexadecan-1-ol (13) | 18.15 | 1.08 | Fatty alcohol | $C_{17}H_{36}O$ | 256 |
| methyl palmitate (15) | 20.61 | 5.51 | Fatty ester | $C_{17}H_{34}O_2$ | 270 |
| Palmitic acid (17) | 21.83 | 13.56 | Fatty acid | $C_{16}H_{32}O_2$ | 256 |
| cis-13-Eicosenoic acid (18) | 23.48 | 1.49 | Fatty acid | $C_{20}H_{38}O_2$ | 310 |
| ethyl linolate (19) | 23.72 | 1.49 | Fatty ester | $C_{20}H_{36}O_2$ | 308 |
| myristylmyristate (21) | 40.88 | 5.06 | Fatty ester | $C_{28}H_{56}O_2$ | 424 |
| Palmityl palmitate (23) | 46.86 | 13.01 | Fatty acid ester | $C_{32}H_{64}O_2$ | 480 |
| Stearyl palmitate (24) | 54.35 | 4.6 | Fatty acid ester | $C_{34}H_{68}O_2$ | 508 |
| ***Total fats = 47.53*** | | | | | |

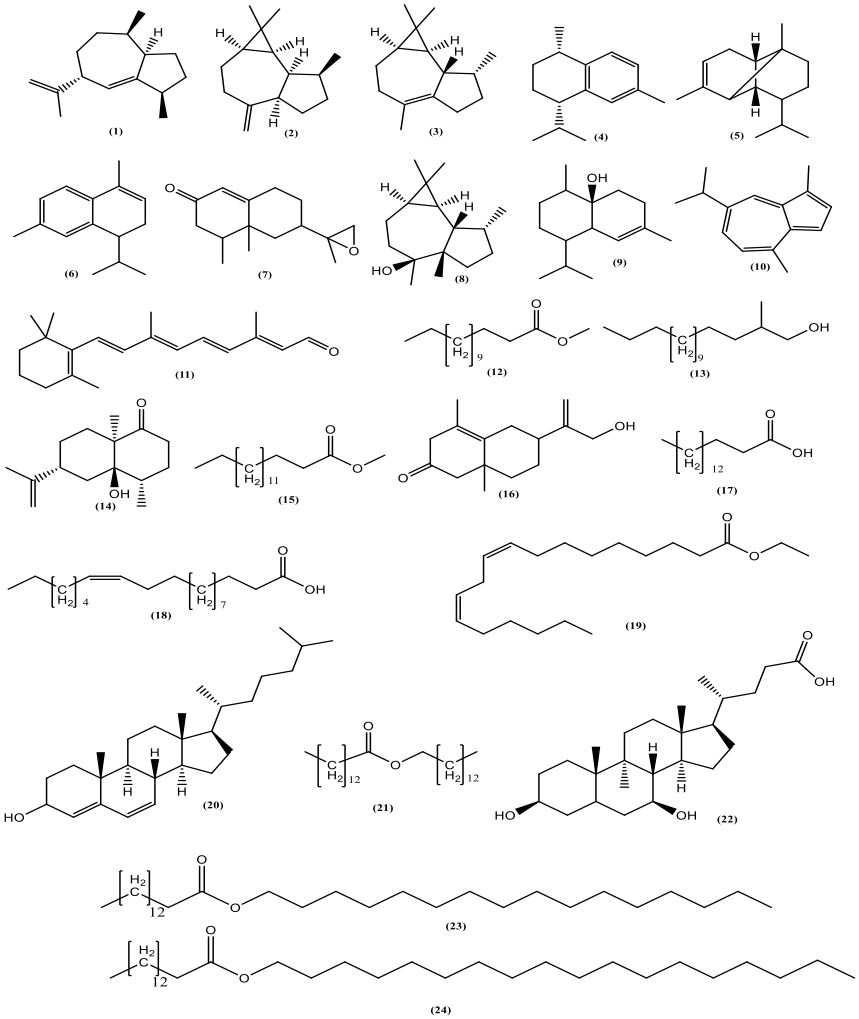

**Figure 7:** Chemical constituents of 20% (ethyl acetate/hexane) *S.convolutum*extract (S)

## 4. Discussion

Carcinogenesis is serious and complex multi-steps process in which an abnormal division of cells takes place leading to development of cancer. There are several kinds of cancer such as prostate, colorectal, breast, uterine and ovary cancer[24].1n 2020, the International Agency for Research on Cancer (IRAC) reported about 10 million deaths out of 19.3 million of cancer- diagnosed patients in 185 countries[25]. Synthetic antitumor drugs like paclitaxel and cisplatin are being used but they are not recommended because their non-selective mechanism and their prolonged usage are associated with significant illness such as bone marrow depression, alopecia and nephrotoxicity [2]. Another artificial anti-cancer drug is Tamoxifen which has high selective mechanism on cancer cells but it's effectiveness as anti-cancer agent is very low and the prolonged use of it may cause uterine and endometrial tumors. As a final result, their side effects are fetal to patients[26]. Viral infections such as influenza, herpes simplex virus(HSV), human immunodeficiency virus (HIV), respiratory syncytialvirus (RSV), andEbola virus (EVD), as well as the coronavirusdisease 2019 (COVID-19), are the main causes for millions of human death worldwide [27]. The severity of viral infection owes to the rapidly genomic mutation of viruses and rapidly spread, making it very difficult to force virus, so finding efficient antiviral drug for treatment of viral infections become abig challenge [22]. Viral mutation leads to viral resistanceso it's necessary to explorenovel antiviral compounds with different mechanismsof action to manage viral infections [28]. Natural products drug discovery become primary focus of researcher especially from marine source because the need to have safer and efficient anti-tumor drugs developed and become really a challenge for medicinal chemists[29]. In this study, 20 % (EtoAc/$CH_2Cl_2$) *sarcophytonconvolutum*extract (S)exhibited invitro anticancer activity against 4 human cancer cell lines; hepatocellular carcinoma cell line (HepG2), human colorectal adenocarcinoma (CaCo2), breast cancer cell line (MCF-7), and pulmonary adenocarcinoma (A549) and the $IC_{50}$ values were 102.73, 100.62, 86.68 and 81.64µg/mL, respectively. Also, antibacterial activity was recorded where, *S. Con*extract has antibacterial activity against *P. aeruginosa* ATCC 15442. As mentioned above,*S. con* extract (S) is rich withsesquiterpenoidsandFatty acid derivativeswhich responsible for biological activity of extract. As mentioned above, fatty acid concentration about 50% in which Palmitic acid and its derivatives accounts for the highest concentration of fatty acid content. Palmitic acid possess a promising anti-tumor efficacy against various malignancy cells, also, Its derivatives play a significant role in tumor resistance processes[30,31]. Sesquiterpene contents represents about 45% of whole extract. Aromandendrene (2) (5.51%), (+)-ledene (3) (5.27%) and (+)-viridiflorol (8) represents half sesquiterpene content. (+)-viridiflorolsesquiterpenoid showed cytotoxic effects against tumor cell lines[32]. ledene oxideshowed cytotoxic effects against human lung carcinoma (H1299) and liver carcinoma (HepG2) cell lines[33]. As final conclousion, the bioactivity of *S.convolutum*extract (S) oweing to effect of combination of all compounds in theextract (S) leading to presence of its synergistic effect.

## 5. Conclusion

Our in vitro study indicates that *S. Convolutum*extract (S) found to be rich source of sesquiterpene and fatty acid derivatives in combination together. This combination enhances the extract with its bioactive features as anticancer and antimicrobial agents. As final conclusion, 20% (ethyl acetate/hexane) *SarcophytonConvolutum*extract (S) is a promising *in-vetro* anticancer and antimicrobial agent. *In-vivo* studies should be done in future in order to study the effect of the extract on mice followed by clinical trials.

## 6. Abbreviations

S: 20% (ethyl acetate/hexane) *SarcophytonConvolutum*extract; MIC: Minimum Inhibitory concentration; ZOI: Zones of inhibitions; HepG2: Hepatocellular carcinoma cell line; CaCo2: human colorectal adenocarcinoma; MCF-7: breast cancer cell line; A549: pulmonary adenocarcinoma; DMSO: Dimethyl sulfoxide; RPMI: Roswell Park Memorial Institute 1640 medium; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5 diphenyltetrazolium

bromide; IC50: Half maximal inhibitory concentration; CC50: The concentration that caused 50% toxicity; SI: The selectivity index; HSV-1: herpes simplex virus ; HAV: hepatitis A virus.

## 7. Conflicts of interest

"There are no conflicts to declare".

## 8. Formatting of funding sources

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## 9. Acknowledgments

Not applicable

## 10. Ethics approval and consent to participate

This article does not contain any studies involving animals or human participants performed by any of the authors.

## 11. Conflict of interest

The authors have declared no conflict of interest.

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