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Chemical Composition and Biological Activity of Diterpenoids from *Plectranthus mutabilis* codd.

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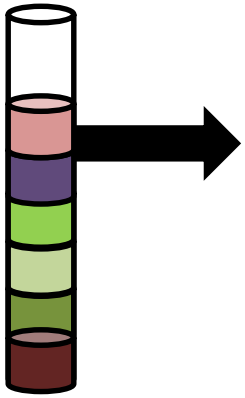
Cytotoxic Activity of Coleon Diterpenoids from *Plectranthus mutabilis* Codd.

Graphical Abstract

Plectranthus mutabilis Codd.

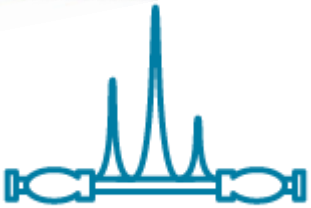
Ultrasound-assisted Extraction method



Bio-guided isolation of the most active extract: *P. mutabilis* Codd.

Structure elucidated

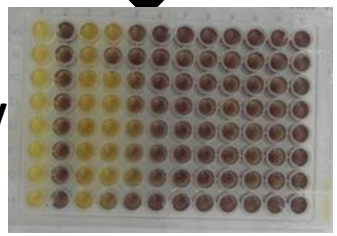
1D- and 2D-NMR



LC/MS

HRMS

Cytotoxicity Study



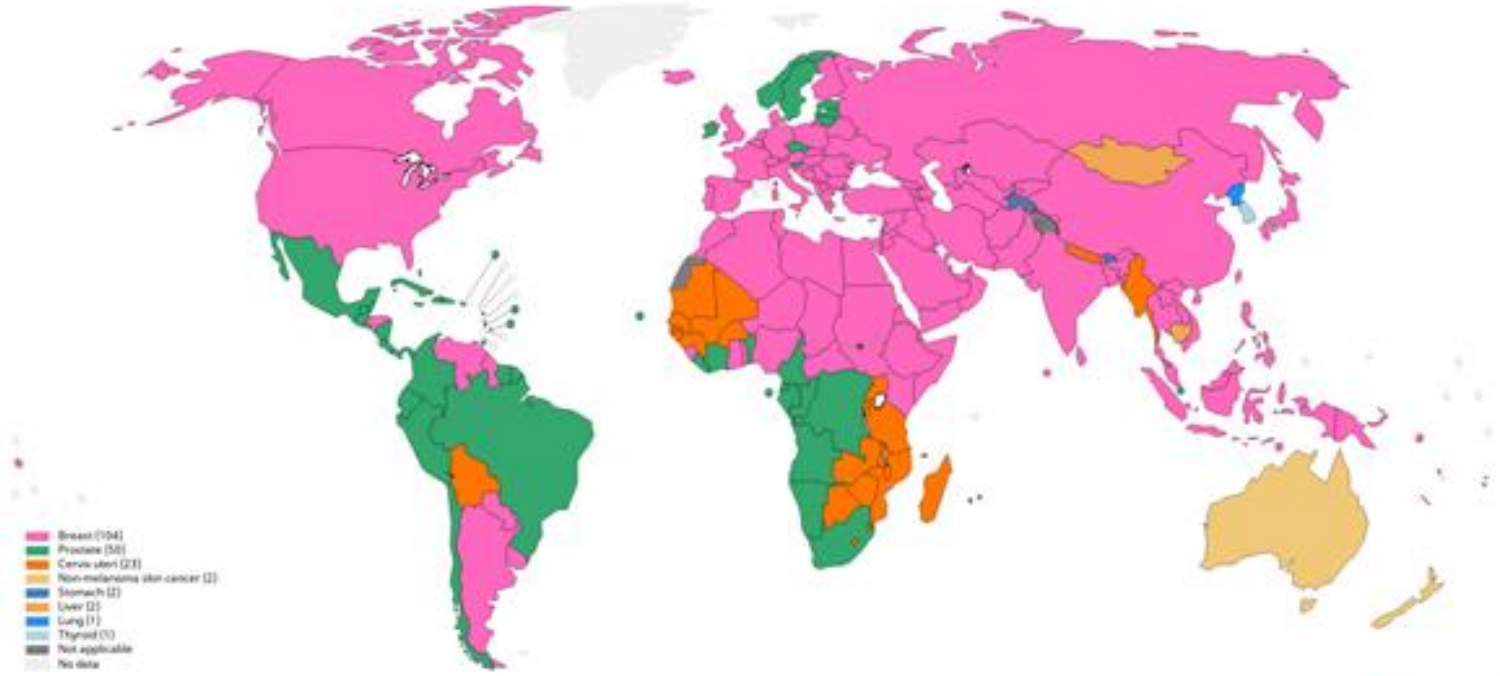
Toxicity study:
- General toxicity (*Artemia salina*)
- Cytotoxicty (Cancer and normal Human cell lines)

Abstract:
Despite the great development in Human medicine, cancer is still a serious threat to public health and consequently, research on new anticancer agents should be continued. Natural products from medicinal plants (e.g., *Plectranthus* species) continue to be a substantial resource to treat different diseases, particularly in developing countries [1, 2]. *Plectranthus* species are rich in diterpenoids, which are reported to be responsible for various pharmacological activities such as cytotoxic activity [1]. *P. mutabilis* Codd. is a perennial succulent herb containing Nepetoidins A and Nepetoidins B in its essential oils and have limited information available in the literature [3].
In this study, we performed an ultrasound-assisted acetone extraction of air-dried *P. mutabilis* whole plant followed by a bio-guided fractionation using the *Artemia salina* general toxicity assay that resulted in the identification of four compounds: Coleon U quinone (**1**), 8α,9α-Epoxycoleon U quinone (**2**), Coleon U (**3**) and 7-hydro,14-deoxycoleon U (**4**) [4]. The cytotoxicity of the isolated compounds and *P. mutabili*s extract was evaluated using a model system of sensitive (NCI-H460) and MDR (NCI-H460/R) cells, along with normal human embryonal bronchial epithelial cells (MRC-5). Studies of modulation of P-gp activity are ongoing to unveil the interaction of these compounds and extract with P-gp.
Keywords: *Plectranthus*, Coleon, Cytotoxicity, P-gP

Introduction

- Cancer is still a serious threat to public health
- Cancer –2nd leading cause of death worldwide
- 18.1 million new cases and
- 1 in 6 deaths is due to cancer in 2018

Top cancer per country, estimated age-standardized incidence rates (World) in 2018, both sexes, all ages

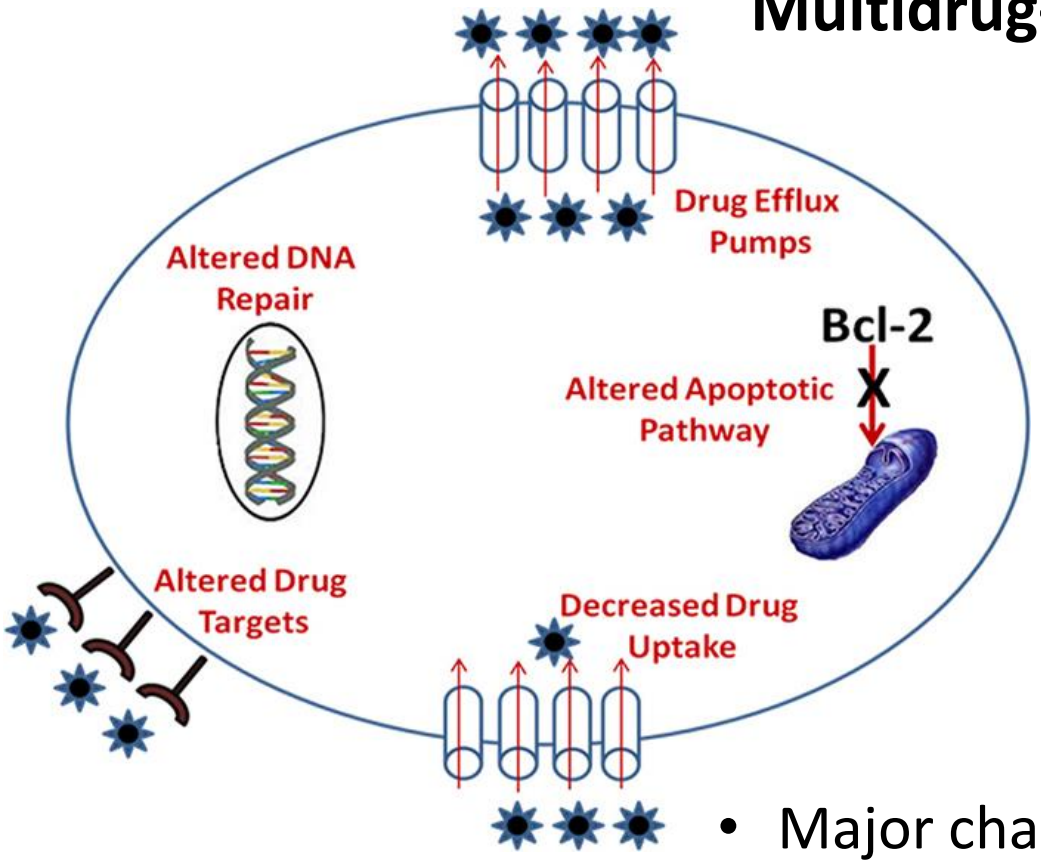


Data source: GLOBOCAN 2018
Graph production: IARC
(http://gco.iarc.fr/today)
World Health Organization

World Health Organization
© International Agency for Research on Cancer 2018

Introduction

Multidrug-resistant (MDR)



- Major challenge to cancer therapy
- Need to develop new reversal MDR agents

Introduction

Plectranthus genus

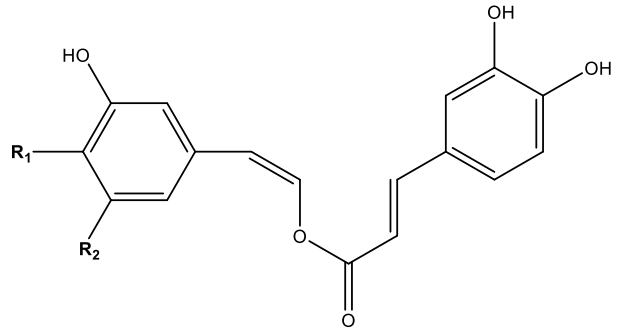
- ❖ Natural products: source of bioactive compounds
- ○ ***Plectranthus* genus (Lamiaceae) uses:**
- ❖ Treatment of different types of cancer

- ○ **Source of bioactive compounds:**
- ❖ abietane-type diterpenoids
- ❖ antibacterial, antifungal and **antitumoral**

Introduction

Plectranthus mutabilis

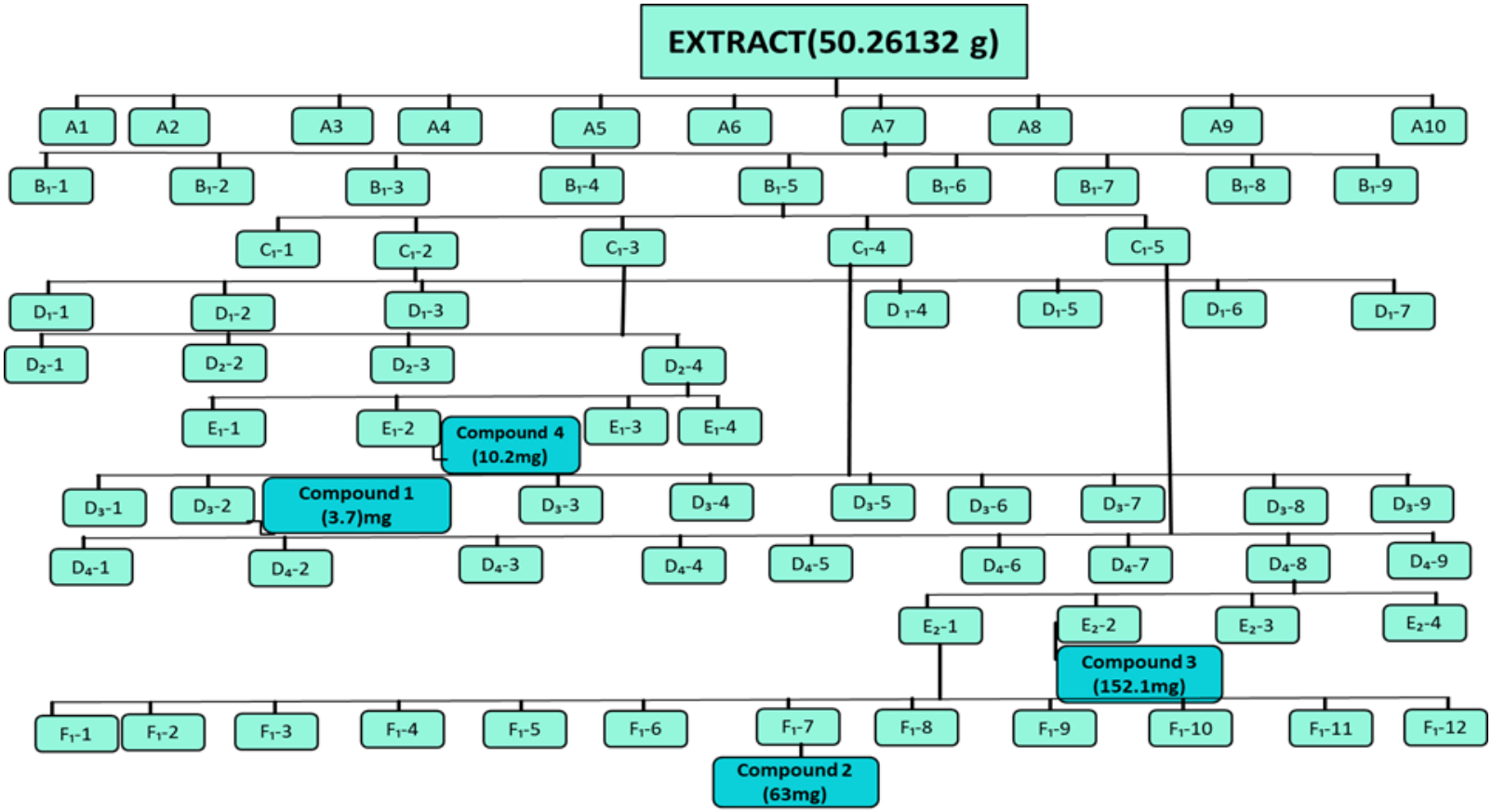
- ❖ Limited phytochemical literature information
- ❖ Chemical constituents in essential oils only reveals:
- ➢ Nepetoidins A and Nepetoidins B



	R_1	R_2
Nepetoidins B	H	OH
Nepetoidins A	OH	H

Grayer *et al*, Phytochemistry ,(2003), 519–528

Bio-guided Isolation of Four Abietane diterpenoids from *P. mutabilis*



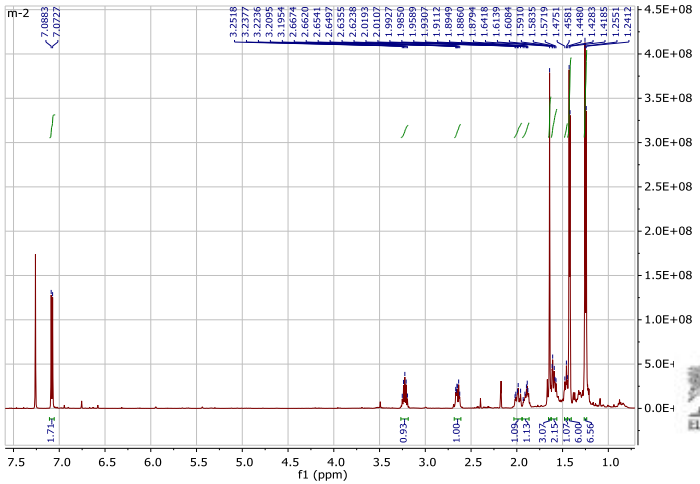
Flash chromatography

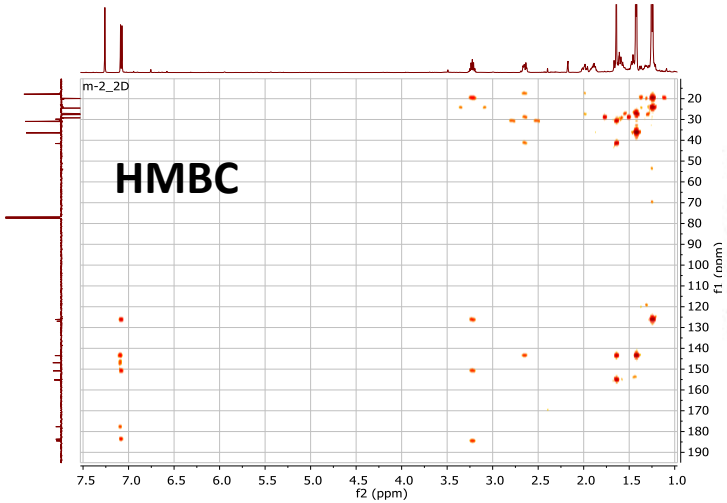
- Stationary Phase: Silica and Polyamid, 100g
- Eluent: increasing polarity

Semi-preparative HPLC

- C18 column (kinetex 5u XB-C18 100A, 250 x 21.2mm)
- 53% aqueous acetonitrile

Characterization of isolated compounds





Structure elucidated

1D- and 2D-NMR

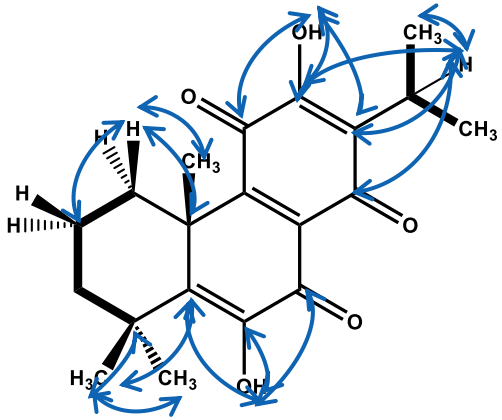
- ^{1}H, ^{13}C, HMBC, HSQC, COSY, NOESY
- LC/MS
- HRMS
- Available Literature

Available online at www.sciencedirect.com
ScienceDirect
PHYTOCHEMISTRY

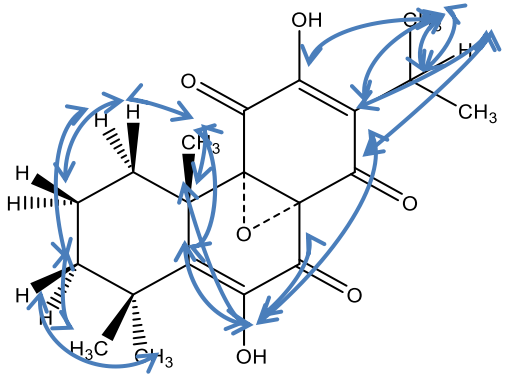
Insect-antifeedant and antibacterial activity of diterpenoids from species of *Plectranthus*

Julia Wellsow, Renée J. Grayer, Nigel C. Veitch, Tetsuo Kokubun, Roberto Lelli, Geoffrey C. Kite, Monique S.J. Simmonds *

Available literature

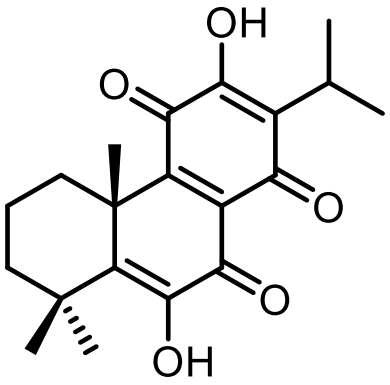


Coleon U quinone (1)



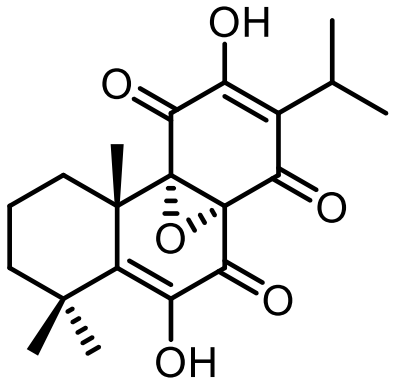
8α,9α-Epoxycoleon U quinone (2)

Results and discussion
Diterpenoids from isolated *P. mutabilis*



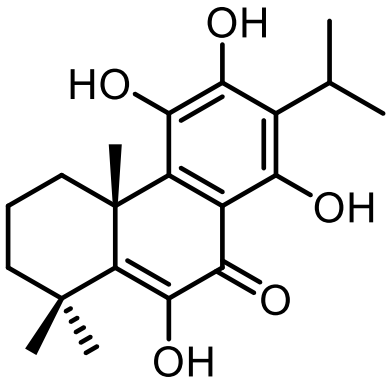
1

Coleon U quinone
MM=344
$[M+H]^+$ m/z = 345
HRMS m/z 345.1711 $[M]^+$ (calcd. for $C_{20}H_{24}O_5$, 345.1697



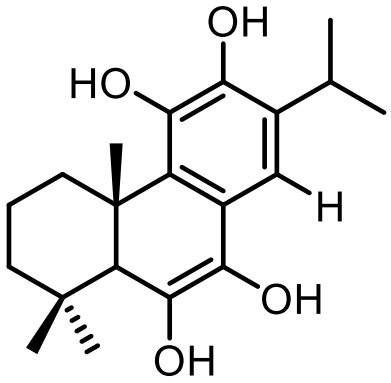
2

8α,9α-Epoxycoleon U quinone
MM=360
$[M+H]^+$ m/z = 361
$[M-H]^-$ m/z = 359
HRMS m/z 361.1658 $[M]^+$ (calcd. for $C_{20}H_{24}O_6$, 359.1502)



3

Coleon U
MM=346
$[M-H]^-$ m/z = 345
HRMS m/z 345.1708 $[M]^-$ (calcd. $C_{20}H_{24}O_5$, 345.1707).

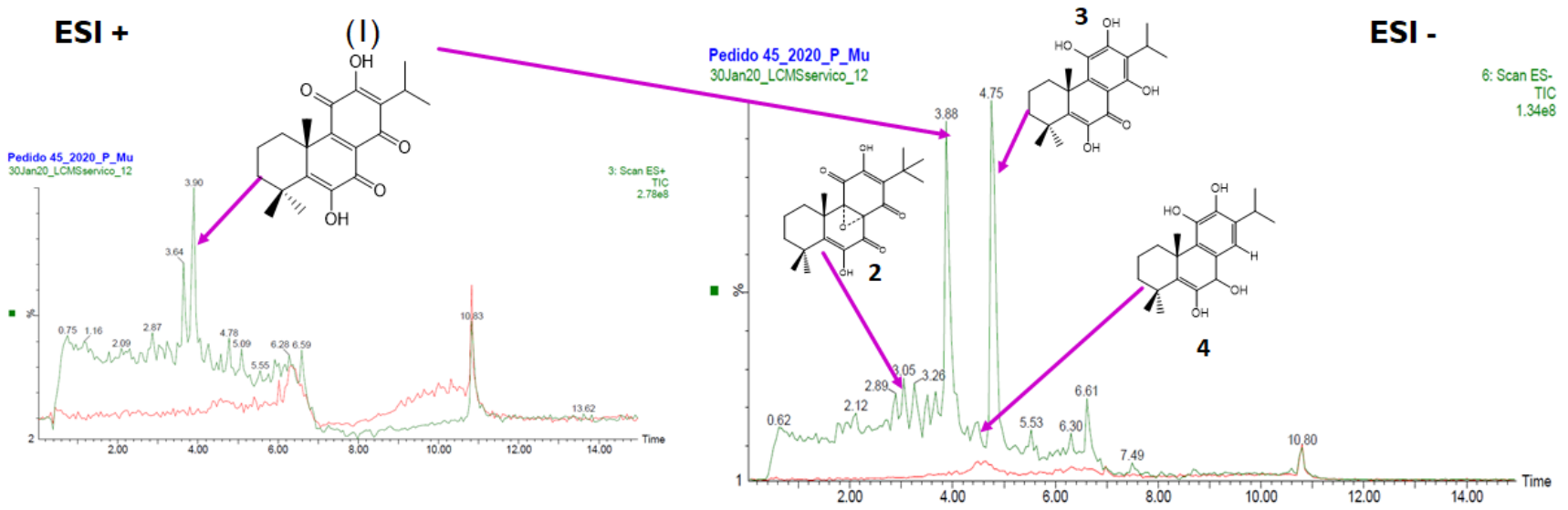


4

7-hydroxy,14-deoxycoleon U
MM=332
$[M-H]^-$ m/z = 331

LC/MS analysis of 4 compounds from *P. mutabilis*

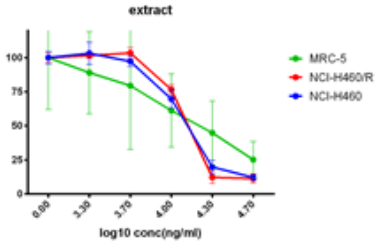
Chromatographic profiles of *P. mutabilis* extract and identification of 4 isolated compounds

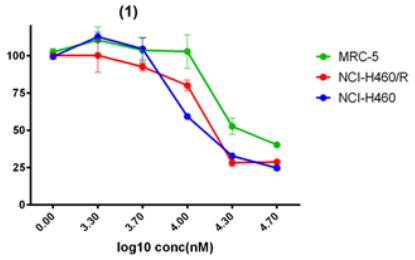


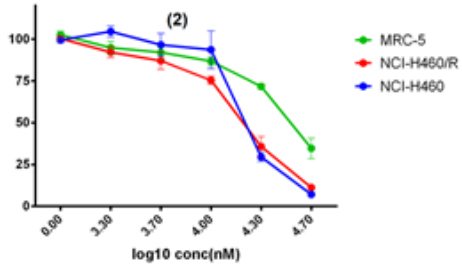
- All the compounds were found to be present in the extract
- Coleon U quinone (**1**) and Coleon U (**3**) seem to be the major compounds in extract

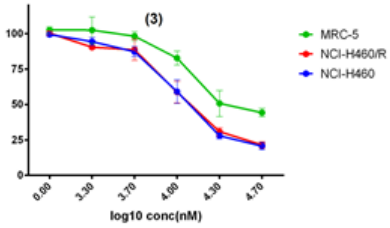
Cytotoxicity study: MTT assay, IC_{50} values in µM

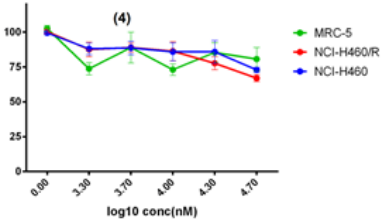
Compounds	NCI-H460	NCI-H460/R	MRC-5
Coleon U Quinone (1)	22.96±0.56	20.37±0.43	44.13±1.19
8α,9α-Epoxycoleon U quinone (2)	20.23±0.59	17.26±0.26	40.22±0.44
Coleon U (3)	14.11±0.19	14.50±0.18	35.47±0.56
Mutabilol (4)	112.58±2.05	81.14±1.13	120.25±4.69
***P. mutabilis* extract**	15.30±0.37	15.66±0.47	16.68±0.69











- Compounds 1, 2 and 3 are selective towards cancer cells
- Compound 4 is not cytotoxic in a given range of concentrations (2 to 50 µM)
- All compounds are not substrates for P-gp

Conclusions

- *P. mutabilis* extract contains: Coleon U quinone, 8α,9α-Epoxycoleon U quinone, Coleon U and 7-hydro,14-deoxycoleon U.
- Coleon U quinone is one of the major compounds in extract
- Compounds 1, 2 and 3 are selective towards cancer cells due to lower IC_{50} in cancer cells than in normal bronchial fibroblasts
- Compound 4 is not cytotoxic in a given range of concentrations (2 to 50 µM).
- All compounds are not substrates for P-gp

Acknowledgments

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