LUNG CANCER: PHLOROGLUCINOL, A NEW STRUCTURAL MOTIVEIN DEVELOPMENT OF CHEMOTHERAPEUTICS

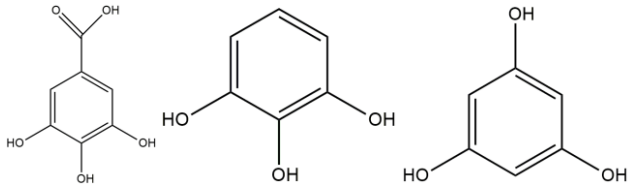
Ana Mijušković

Supervisors: Boris Pejin, PhD, Vesna Kojić, PhD and Dimitar Jakimov, PhD

Regional Centre for Talented Youth Belgrade II, Belgrade, Serbia, anamijuskovic2000@gmail.com

1. Introduction

According to available statistical data, lung cancer globally represents the most common oncological disease [1]. Therefore, more effective chemotherapeutics than existing ones, preferably those of natural origin, are more than welcomed. Gallic acid is mostly present in berry fruits and grapes. In literature, its antitumor activity is particularly in relation to liver cancer [2].The aim of this study was to determine both the cytotoxic activity of total phenolics present in the seeds of selected grape types (at the extract level) and individual phenolic compounds (Gallic Acid, Pyrogallol and Phloroglucinol; **Figure 1**) on the epithelial cells of adenocarcinoma A-549 at *in vitro* conditions. As the most active sample, Phloroglucinol was also screened*in vitro* for its genotoxic properties as well.



A **B** **C**

*Figure 1. **A**– Gallic Acid **B**–Pyrogallol **C**– Phloroglucinol*

2. Material and Methods

Autochthonous *Prokupac* and international *Merlo* and *Cabernet Franc* were selected as the starting grape varieties for the preparation of methanol extracts by a standard method adapted to the extraction of dry samples [3]. The content of total phenolics was evaluated by Folin-Ciocalteu method. The cytotoxic activity and genotoxic properties were determined by colorimetric MTT (preceded by the DET test) and micronucleus tests, respectively. Both the cell lines (malignant A-549 and healthy /normal/ MRC-5) and all chemicals used within this study were purchased from commercial suppliers. Drugs Doxorubicin and Cisplatin were used as positive controls. Finally, the sample of brown algae *Fucus vesiculosus* was kindly provided by a contact from Trinity College Dublin, Dublin, Republic of Ireland.

3. Results and Discussion

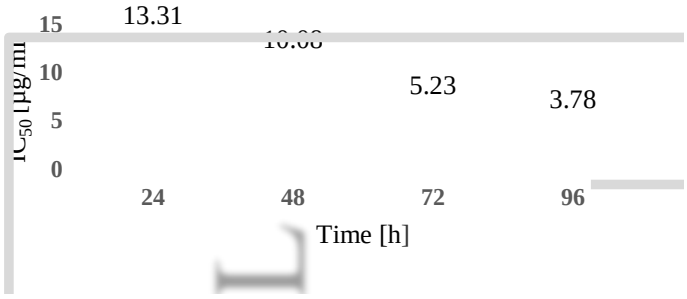
According to the cytotoxic activity on the malignant A-549 cells (IC_{50} = 21.37 μg/mL) and total phenolics content (104.05 g Gallic Acid equivalents/kg d.w), methanol extract of the grape variety *Prokupac* stood out. One the other hand, Gallic Acid, known as the most abundant hydroxybenzoic acid in grape seeds, did not show any significant effect on A-549 cells (**Table 1**) thus cannot be considered as one of the extract bioactive principles. In fact, Pyrogallol, its structural element, exhibited 10-fold higher cytotoxicity than Gallic Acid. Finally, Phloroglucinol, a Pyrogallol isomer, was found to be the most active phenolic compound on A-549 cells, with no cytotoxicity on healthy MRC-5 cells. In comparison, Doxorubicin and Cisplatin were significantly cytotoxic on the both cell lines. Furthemore, the results of the micronucleus test have pointed out the lack of genotoxic properties for Phloroglucinol, unlike Doxorubicin. Finally, *F. vesiculosus* extract rich in Phloroglucinol and its derivatives displayed a potent antitumour activity (IC_{50}=3.7μg/mL) after 96h on A-549 cells (**Graphic 1**), not affecting MRC-5 cells (IC_{50}> 1000 μg/mL) at the same time point.

Table 1. Cytoxic activity of selected phenolic compounds and positive controls

IC_{50} [μM]	GA*	PYR*	PHLOR*	DOX*	CISPLAT*
A-549	200	20.05	4.07	0.001	11.94
MRC-5	>1000	>1000	>1000	0.1	14.34

* GA – Gallic Acid; PYR – Pyrogallol; PHLOR – Phloroglucinol; DOX – Doxorubicin; CISPLAT – Cisplatin

Graphic 1. Cytotoxic activity of the brown alage Fucus vesiculosus extract



4. Conclusion

Taken all together, the chemical structure of Phloroglucinol should take a special place in the design of a new lung chemotherapeutic. Therefore, organisms rich in Phloroglucinol and its derivatives, such as the screened one here of brown algae *Fucus vesiculosus* could be used as possible dietary supplements with anti-lung-cancer activity. Further research efforts will be directed towards development of semi-synthetic derivatives of Phloroglucin, tautomeric form of Phloroglucinol possesing ketone character, with Hydrazine or Hydrazine-like compounds.

5. Literature

[1]American Cancer Society 2019, https://www.cancer.org [31st January 2019]
[2] P. Sun et al., Oncol Lett. 11 (2016) 150–158
[3] A. Pavlović et al., J Agric Food Chem. 61 (2013) 4188–4194