Anticancer Hybrid Combinations with phenolic compounds

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1. Introduction: Different types of treatments are been employing to overcome cancer, which is characterized by abnormal cell growth involving cell division without control. However, their usually lack of selectivity and the development of resistance result in limited efficacy or ineffectiveness of the therapies. For these reasons, the seeking of new treatment options for this disease is necessary. Nowadays, the acknowledge bioactive properties of some secondary metabolites such as polyphenols, have made antitumour hybrid combinations a promising therapeutic approach.

2. Objectives: This review provides an overview into anticancer hybrid combinations involving several phenolic compounds, focusing on their multi-target mechanisms of action and synergistic effects. It aims to contribute for the scientific validation of this type of phytopharmaceuticals as potential adjuvants in cancer (chemo)therapy.

3. Materials and Methods: Bibliographical review using the information compiled from books and electronic databases (Web of Science, PubMed and other scientific databases).

4. Results:

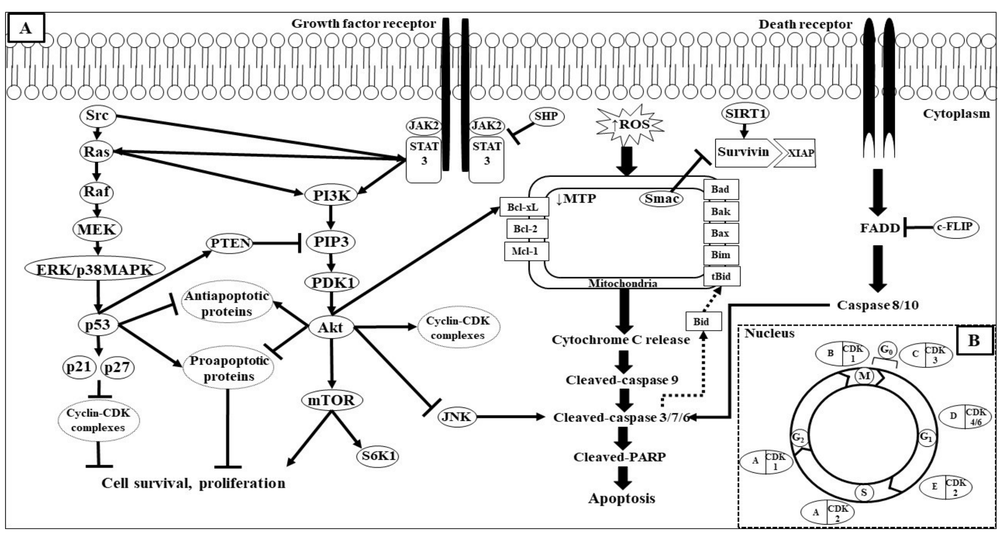
4.1. What are anticancer hybrid combinations?

- Anticancer hybrid combinations are the therapeutic combination of synthetic drugs with chemically defined constituents from plants (secondary metabolites) aiming to increase the pharmacological activity of the formulation and, simultaneously, reduce the toxic side-effects of the drugs, interaction known as synergy. Example: Combinations of polyphenols with alkylating agents to enhance the activity of the drug in leukaemia cell lines.
- The secondary metabolites used in these combinations are mainly plant-derived phenolic compounds and terpenoids.
- Both compounds are characterized by an extensive structural diversity associated with a range of biological activities.
- "Hybrid combination" term was introduced for the first time in 2017 by H. Wagner and T. Efferth.
- Once synergistic hybrid combinations are identified, it is relevant to probe their mechanism(s) of action.

4.2. Multi-target mechanisms

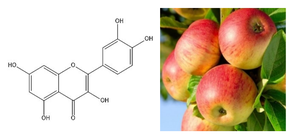
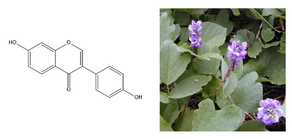
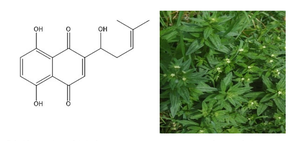
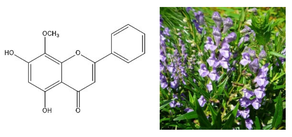
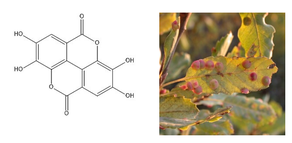
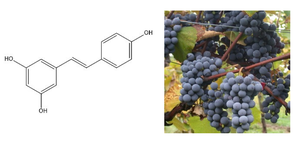
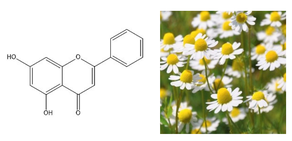
- Multi-target therapies involve the combination of different components that are not directed against a single target but instead are able to impact multiple targets simultaneously, including enzymes, substrates, metabolites, nucleic acids, receptors, transporters, cellular organelles and/or signal cascades in a synergistic way.
- Multi-target therapies are necessary for treating multifactorial diseases such as cancer.
- The main type of hybrid therapies comprises the combinations that act on different targets belonging to the same signalling pathway. This allows them to modulate multiple carcinogenic signalling pathways and thus limit the appearance of associated compensatory signalling feedback loops.

4.3. Scheme of the main multiple signaling pathways involved in apoptosis and cell cycle regulation (cellular processes often deregulated in cancer) that can be modulated by anticancer hybrid combinations:



A) Schematic diagram of intrinsic and extrinsic apoptosis, and the main cellular signalling pathways affected by the hybrid combinations described. B) Representation of the cell cycle and its regulation by cyclin(A-E)-cyclin-dependent kinase (CDK) complexes.

4.4. Examples of combinations that act on different targets belonging to the same signalling pathway

Type of cancer (tumoral cell lines)	Phenolic compound / Plant origin	Drug	Affected biological process/signalling pathway	Down-regulated targets	Up-regulated targets
Astrocytoma (MOGGCCM)	 Quercetin (*Malus domestica* Borkh.)	Temozolomide	↑Autophagy (5 μM quercetin)	-	LC3-II
			↑Intrinsic apoptosis (30 μM quercetin)	MTP, HSP27/72	Caspase-3, Cyt C
Breast (MCF-7, MDA-MB-231)	 Daidzein (*Pueraria montana var. Lobata* (Willd.) Sanjappa & Pradeep)	Centchroman	↑Intrinsic apoptosis	MTP, Bcl-xL in MDA-MB-231 cells	ROS, Bax, caspase-9/-3/-7, PARP
			Cell cycle	-	Sub-G0/G1 cells
			↓PI3K/Akt/mTOR	PI3K, p-Akt, pmTOR in MCF-7 cells	-
Burkitt's lymphoma (Namalwa, Raji)	 Shikonin (*Lithospermum erythrorhizon* Siebold & Zucc.)	Doxorubicin	↑Apoptosis	-	Caspase-3, PARP
Gastric (BCG-823)	 Wogonin (*Scutellaria baicalensis* Georgi)	Oxaliplatin	↑Intrinsic apoptosis	MTP	$ONOO^-$
			↓Raf/MEK/ERK	-	p-JNK
			↑Autophagy	p-ULK1	LC3-II
Human Hepatocellular Carcinoma (HepG2, SMMC-7721)	 Ellagic acid (*Quercus infectoria* G.Olivier)	Doxorubicin or Cisplatin	↑Intrinsic apoptosis	-	PARP, Caspase-3,-9, Cyt C
			↑Autophagy	-	LC3-II
Multiple myeloma (LP-1, U266, MM.1S, MM.1R)	 Resveratrol (*Vitis vinífera* L.)	Carfilzomib	↑Intrinsic apoptosis	p-p38	ROS, caspase-3/-9, PARP, HMOX1
			Cell cycle	p-CDK4, p-cyclin D1	G2/M cells
			↓SIRT1/survivin	SIRT1, survivin	Smac
Non-small cell lung cancer (A549, xenograft mouse model)	 Chrysin (*Matricaria recutita* L.)	Docetaxel	↑Extrinsic/intrinsic apoptosis	Bid	TRAILR-1/-3/-4
			Apoptosis/cell proliferation	-	p53, p21, p27, IGFBP-4/-6

5. Discussion and conclusion: Hybrid combinations comprising synthetic or semi-synthetic anticancer drugs and secondary metabolites from medicinal plants are a promising therapeutic strategy due to their synergistic effect and multi-target mechanisms of action. Both characteristics contribute to reduce cancer resistance to different treatments and minimize adverse effects, while simultaneously showing selectivity for tumour cells and potentiate the activity of the drug, which makes hybrid combinations an interesting prospective option to cure cancer.

Translation of anticancer hybrid combination therapy into clinical practice is therefore dependent on the development of an adequate regulatory framework and mostly on further preclinical and clinical studies.

6.References: **[1]** Domínguez-Martin EM, Diaz-Lanza AM, Faustino CMC (2018) Curr Pharm Des 24, 4312-4333. **[2]** Wagner H, Efferth T. (2017) Phytomedicine, 37, 1-3. **[3]** Mahbub AA, Le Maitre CL, Haywood-Small S, Cross NA, Nicola Jordan-Mahy N (2019) Oncotarget 10, 4570-86. **[4]** Zhong C, Qiu S, Li J, Shen J, Zu Y, Shi J, Sui G (2019) Phytomedicine 59, 152921.

*This work is based on reference **[1]**. which has been updated with new published references on phenolic compounds-based anticancer hybrid combinations.

5th International Electronic Conference on Medicinal Chemistry
1-30 November 2019

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