Fitoterapia 129 (2018) 383–400

Contents lists available at ScienceDirect

Fitoterapia

journal homepage: www.elsevier.com/locate/fitote

Review

Sensitization of tumor cells to chemotherapy by natural products: A systematic review of preclinical data and molecular mechanisms

Raimundo Gonçalves de Oliveira Júnior[a], Alves Ferraz Christiane Adrielly[b], Jackson Roberto Guedes da Silva Almeida[b], Raphaël Grougnet[c], Valérie Thiéry[a], Laurent Picot[a,*]

[a] UMRi CNRS 7266 LIENSs, University of La Rochelle, 17042 La Rochelle, France
[b] Center for Studies and Research of Medicinal Plants, Federal University of San Francisco Valley, 56306-000 Petrolina, Brazil
[c] UMR CNRS 8638 Laboratory of Pharmacognosy, Paris Descartes University, 75006 Paris, France

ARTICLE INFO

Keywords:
Cancer
Chemotherapy
Chemosensitization
Drug resistance
Natural products

ABSTRACT

Purpose: Tumor cells are spontaneously or adaptively resistant to chemotherapeutic drugs, eventually leading to the selection of multiresistant cells responsible for tumor growth and metastasis. Chemosensitization of tumor cells to conventional drugs using non-toxic natural products is a recent and innovative strategy aiming to increase the cytotoxic efficiency of anticancer drugs, limit their toxic side effects and delay the appearance of acquired chemoresistance. This systematic review summarizes data obtained from preclinical studies reporting the use of natural products to sensitize tumor cells to chemotherapeutic agents. It also details the cellular and molecular mechanisms involved in chemosensitization.

Design: Search terms were combined and used to retrieve English language reports in PubMed, Science Direct and Scopus databases, published until October 2017. All articles were carefully analyzed and data extraction was conducted through standardized forms. Methodological quality assessment of *in vivo* studies was also performed.

Results: From a total of 669 articles surveyed, 104 met the inclusion criteria established. The main studied compounds as chemosensitizers were phenolic derivatives (26.9%) and flavonoids (17.3%). Most reports were authored by researchers from China (33.7%) and USA (26.9%). A large number of articles were published from 2011 to 2015 (50.0%), suggesting that the use of natural products as chemosensitizers is a recent issue. *In vivo* studies were conducted mainly using xenograft models, which were considered of moderate methodological quality.

Conclusion: Several natural products, belonging to diverse chemical families, are potent chemosentisizers in tumor cells enhancing the cytotoxicity of conventional drugs. These molecules usually have a pleiotropic effect on different molecular targets, acting on several cellular and molecular processes with low selectivity. All studied molecules were obtained from terrestrial plants and major developments should arise from future studies, considering the chemodiversity of molecules purified from other terrestrial taxa and marine organisms.

1. Introduction

Cancer is one of the most impactful diseases of the 21st century, affecting populations of diverse social, ethnic and economic characteristics. Although the genetic, epigenetic and pathophysiological mechanisms of cancer have been well described in recent years, cancer still represents the second cause of death in developed countries after heart disease [1,2].

To ensure their survival and proliferation, cancer cells acquire differentiated abilities compared to normal cells. In the development of malignant tumors, they may present constitutively active proto-oncogenes, which predisposes to carcinogenesis, maintaining proliferative signaling pathways active [3]. In addition, expression of tumor suppressor genes is usually decreased and the cell acquires sufficient autonomy to continue multiplying without the need for growth factors. Tumor cells also have replicative immortality mechanisms [4] and greater resistance to cell death mediated by the regulation of anti and pro-apoptotic proteins [5]. For tumor maintenance and progression, they stimulate the production of angiogenic factors and modulate cellular metabolism in order to obtain more nutrients [3,6].

In this sense, chemotherapy is one of the main alternatives for cancer treatment, using molecules capable of inhibiting proliferative signaling pathways, replicative immortality mechanisms and angiogenesis, besides inducing apoptosis of tumor cells [7–10]. However, the

* Corresponding author at: UMRi CNRS 7266 LIENSs, Université de La Rochelle, Curie B101 Faculté des Sciences et Technologies, Avenue Michel Crépeau, 17042 La Rochelle, France.
E-mail address: laurent.picot@univ-lr.fr (L. Picot).

https://doi.org/10.1016/j.fitote.2018.02.025
Received 26 January 2018; Received in revised form 19 February 2018; Accepted 20 February 2018
Available online 21 February 2018
0367-326X/

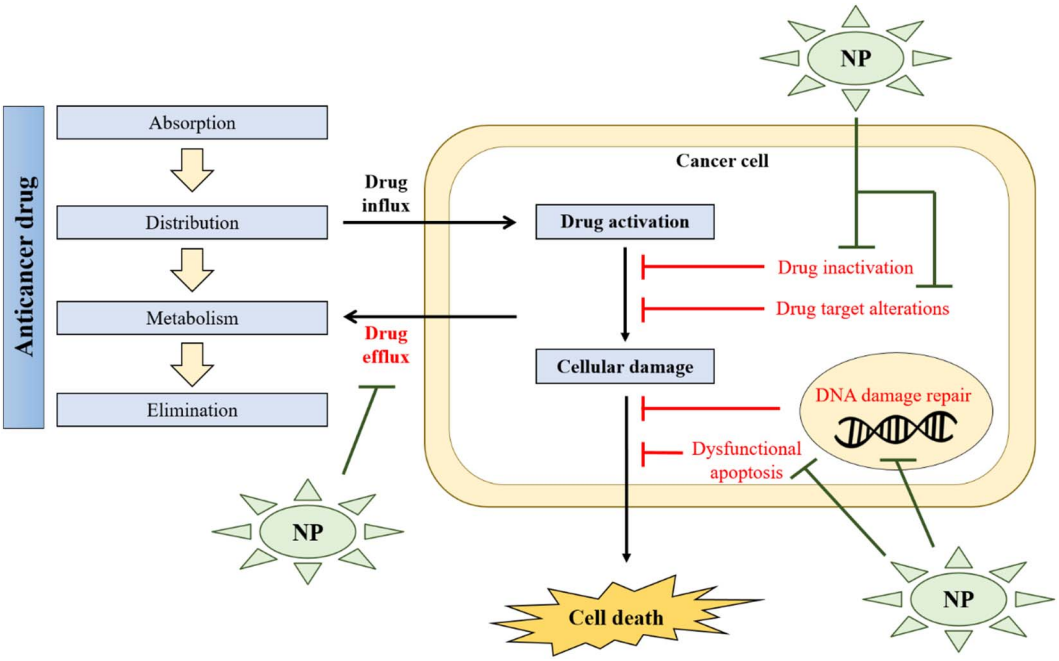

Fig. 1. General drug resistance mechanisms implicated in cancer therapy and possibilities of intervention of natural products (NP) as chemosensitizer agents.

efficacy of conventional chemotherapeutics has been limited by drug resistance mechanisms [11]. Several studies have recognized that tumors exhibit a high degree of molecular and genetic heterogeneity, making them adapted to the usual cytotoxic agents. Unsuccessful treatments have been attributed to increased rates of drug efflux, alterations in drug metabolism (drug inhibition and degradation), cell death inhibition, epigenetic factor and mutations of drug targets (Fig. 1). These mechanisms can act independently or in combination and through numerous signaling pathways [11–13].

A wide variety of natural compounds has been reported for cancer therapy [14,15]. Natural products are an inexhaustible source of molecules with unique structural models and innovative mechanisms of action. In fact, natural compounds can be used in a versatile manner, especially in cancer management: a) as chemotherapeutic agents [16,17]; b) in cancer prevention (chemopreventive agents) [18,19]; c) or improving the effectiveness of conventional chemotherapy (chemosensitizer agents) [20].

Most of the identified chemosensitizer natural compounds are phytochemicals, which are classified as phenolic derivatives, flavonoids, alkaloids, carotenoids, terpenoids, quinones, saponins and steroids depending on their molecular structure [20,21]. In general, these molecules act by increasing the residence time of chemotherapeutics in tumor cells, inducing cell death by up-regulation of pro-apoptotic targets, promoting DNA damage or regulating the expression of altered and unaltered drug targets (Fig. 1). When associated, these mechanisms enhance the cytotoxic effect of anticancer drugs, promoting a synergistic effect even in cells with acquired resistance [22–24].

The present systematic review was designed to summarize and analyze reports involving the use of natural products as chemosensitizers. Our focus was on preclinical studies (*in vitro* and *in vivo* approaches) in order to demonstrate to readers how these experimental models can contribute to the achievement of alternative strategies for cancer therapy.

2. Materials and methods

2.1. Search strategy

A systematic review was conducted through a literature search performed in October 2017 and included all reports published to date. This literature search was performed on specialized databases (PubMed, Science Direct and Scopus) using different combinations of the following keywords: chemosensitization, cancer, tumor, natural products, phytotherapy, medicinal plants, marine products and marine drugs. We did not contact investigators and we did not attempt to identify unpublished data. This systematic review was performed in accordance with the criteria described on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25].

2.2. Study selection

Manuscript selection was based on the inclusion criteria: pre-clinical (*in vitro* and *in vivo*) studies involving the use of natural compounds/secondary metabolites as chemosensitizer agents of tumor cells to chemotherapeutic drugs, as well as pre-clinical (*in vitro* and *in vivo*) studies involving associations/combinatorial treatment between natural compounds/secondary metabolites and conventional chemotherapeutic drugs for antitumor therapy; only articles published in English and containing keywords in the title or abstract were selected. Other review articles, meta-analysis, abstracts, conferences, editorials/letters, case reports, conference proceedings, manuscripts without full text available or articles that did not meet the inclusion criteria were excluded from this systematic review. Studies involving extracts, fractions, synthetic or semisynthetic derivatives were also excluded.

For the selection of the manuscripts, two independent investigators (RGOJ and CAAF) first selected the articles according to the title, then to the abstract and finally through an analysis of the full-text publication. In cases of non-consensus, a third independent review was consulted (JRGSA). The selected articles were carefully reviewed with the purpose of identifying and excluding the reports that did not fit the criteria described above. Additional papers were included in this review after the analysis of all references from the selected articles.

2.3. Data extraction

Data were collected and examined by the authors using standardized forms. The information from the selected manuscripts on studied natural compounds, experimental models, associated chemotherapeutic