Zoopharmacology

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Zoopharmacognosy is the multidisciplinary approach of the self-medication behavior of many kinds of animals. Recent studies showed the presence of antitumoral secondary metabolites in some of the plants employed by animals and their use for the same therapeutic purposes in humans. Other related and sometimes confused term is Zootherapy, which consists on the employment of animal parts and/or their by-products such as toxins, venoms, etc., to treat different human ailments. Therefore, the aim of this work is to provide a brief insight for the use of Zoopharmacology (comprising Zoopharmacognosy and Zootherapy) as new paths to discover drugs studying animal behavior and/or using compounds derived from animals.

Keywords: zoopharmacology ; zoopharmacognosy ; zootherapy ; cancer ; multidrug resistance (MDR) ; collateral sensitivity ; oncotherapy

1. Introduction

Cancer comprises a group of diseases characterized by abnormal cells grown without control, with the potential to invade and to spread through the body [1]. Nowadays, although all the therapeutic options available (surgery, radiotherapy, monotherapy, and polytherapy combination regimens that can include the simultaneous use of biological drugs) can reduce tumor size and increase life expectancy [2][3], cancer is still considered one of the main causes of morbidity and mortality worldwide according to the World Health Organization (WHO) [4]. This is not only due to new cases or relapses but especially because tumors are gained cross-resistance to several unrelated chemotherapeutic agents, developing a multidrug resistance (MDR) phenotype, ultimately remain the second cause of death in developed countries [3][5].

Recent evidence points toward stem-like phenotypes in cancer cells, promoted by cancer stem cells (CSCs), as the main culprit of cancer relapse, resistance to radiotherapy, hormone therapy, and/or chemotherapy, and metastasis. Many mechanisms have been proposed for CSC resistance, such as drug efflux through ABC transporters, microenvironment modulation, epigenome, exomes, overactivation of the DNA damage response, apoptosis evasion, increased unfolded protein response (transforming the cells particularly susceptible to endoplasmic reticulum stress and mitochondrial damage), autophagy deregulation, metabolic alterations, prosurvival pathways activation, and/or cell cycle promotion [3]. These mechanisms are still not completely understood and could occur simultaneously [6]. Nonetheless, targeted therapy toward these specific CSC mechanisms is only partially effective to prevent or abolish resistance, suggesting underlying additional causes for CSC resilience [3].

This resistance can be (a) intrinsic or (b) acquired, being the former caused by pre-existing factors of the tumor that are present before any treatment administered, making consequently certain treatments useless at non-toxic doses. The latter appears to be a relatively common issue throughout the administration of treatment and seems to be the main perpetrator of treatment failure in cancer patients, usually after a relapse. Increasing evidence demonstrates that cells with acquired resistance to a specific drug are prone to exhibit cross-resistance to other chemotherapeutics. This implies the existence of common mechanisms of resistance, which may be independent of the particular action of the chemotherapeutic agent. Importantly, clinical evidence shows that phenotypes of resistance can be reverted to a sensitive phenotype and suggests that cancer-associated genetic alterations are not the only players in resistance. Cancer treatments should target not only the resistance mechanisms already present in the bulk of cancer cells but also those activated in CSCs [3].

The influence of genetics and the environment on cell evolution was suggested to affect individual cells at various levels. Modulation of the CSC epigenome, with the acquisition of undifferentiated, pluripotent, and drug-resistant phenotypes, occurs preferably when CSCs are exposed to environmental stressors, such as inflammation, toxic compounds (including drugs), and/or radiation [3]. It may be possible that some nuclear medicine cancer diagnostic and therapeutic techniques favoring autophagy resulting in the development of resistance [7].

2. Combating Drug Resistance

To combat drug resistance, there are two main strategies: (1) Drugs with novel modes of action to bypass resistance to established drugs or (2) inhibitors of resistance mechanisms for resensitization of tumor cells [8]. The most general approach has been the development of P-glycoprotein (P-gp) inhibitors to co-administer with anticancer drugs [6]. This consists of the pharmacological blockage of drug transporters such as P-gp (a type of ABC transporter) [8], that can lower intracellular drug concentration by expelling the drug from cancer cells [5]. However, despite their great in vitro success, there is no P-gp inhibitor currently available for clinical use [6].

Therefore, novel forms of treatment are seeking and have been purposed to overcome this problem, such as the use of hybrid combinations that consist of the association of anticancer drugs with bioactive phytochemical constituents of plant extracts [2]. Recently, it has been hypothesized that natural products, such as marine drugs, may deliver promising lead compounds for the development of collateral sensitive anticancer drugs. The phenomenon of collateral sensitivity consists of the hypersensitive to specific drugs by tumors with cross-resistance to numerous cytostatic drugs [8]. Although many hypotheses have been proposed, the mechanism of collateral sensitizing compounds remains unclear; nonetheless, they seem to be related to diverse biochemical mechanisms. A recent work assessed the ability of the macrocyclic diterpene plant derivatives as collateral sensitizing compounds in human tumor gastric (EPG85-257), pancreatic (EPP85-181), and colon (HT-29) cell models (drug-sensitive and drug-resistant sublines) [6].

These recent therapeutic proposals evidence of the continuing natural products playing a role in drug discovery and development [9]. A comprehensive review of human drugs introduced since 1981 suggests that, from 847 small molecule-based drugs, 43 were natural products, 232 were derived from natural products (usually semi-synthetic), and 572 were synthetic molecules. However, 262 of the 572 synthetic molecules had a natural product-inspired pharmacophore or could be considered natural product analogues [10]. Besides, more than 60% of current anticancer drugs have their origin from natural sources [9].

The study of natural products has been named as Pharmacognosy, which is the multidisciplinary science that studies the physical, chemical, biochemical, and biological properties of natural drugs and drug substances from plants, animals, fungi, and microorganisms for new drug discoveries [11].

Historically, natural medicines have been used to enhance human and veterinary health since immemorial times as it has been compiled in ancient tales, scriptures among other historical literature. All these texts claim the use of natural remedies to solve first health troubles in different parts of the world [11].

One of the potential areas of research in the field of Pharmacognosy is Ethnopharmacology [11]. This term coined in 1967, consists of the scientific approach to study the biological activities (beneficial or toxic effects) of any traditional preparation used by humans, using observation, description, and experimental research. Nowadays, this area has been greatly expanded, covering a wide range of topics based on anthropological, historical, and other socio-cultural studies [12].

In this regard, although plant-derived products have dominated human pharmacopeias for thousands of years, it also appeared that people from traditional societies learned from animals about the medicinal value of some plants that may not otherwise have been considered to be medicinal. This field is known as Zoopharmacognosy and consists of investigating the self-medication behaviors of animals [13].

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