Austin Therapeutics

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Editorial

Lipid Colloidal Systems: A Strategy to Deliver Natural Bioactive Compounds

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Received: December 11, 2014; **Accepted:** December 12, 2014; **Published:** December 12, 2014

Editorial

The lifecycle of a pharmaceutical product begins with the initial discovery of potential new therapeutic candidates. In this stage, many of these candidates are based on natural products due to their well documented beneficial effects on human health [1]. Once natural products often have complex structural features and, generally, their bioactivity is tightly correlated with their chemical structure, the continuous advances in chemical synthetic methodology have offered practical access to the so called nature-identical materials (i.e. natural substances produced synthetically in an identical molecular form) [2]. Therefore, natural products can be used as clinically useful therapeutic compounds, as starting materials to produce synthetic drugs, or as guide compounds from which a totally synthetic drug is developed, avoiding interactions between different compounds present in botanical preparations [2]. The exploitation of these synthetic derivatives in the development of new pharmaceutical products is a promising field, requiring interdisciplinary research groups like chemists, pharmaceutical technologists, biochemists, toxicologists, pharmacologists.

One of the most promising examples of natural sources of therapeutic bioactive compounds is the flavonoids. I focused my short revision on this class of compounds. They are heterocyclic polyphenolic compounds which are broadly distributed in plants and dietary components (e.g. fruits, olive oil, vegetable, tea, red wine) and, therefore, are believed to be non-toxic [3]. A close relationship between the chemical structure of flavonoids and *in vitro* biologic activity are reported in the literature, suggesting that their basic structure can be chemically modified to increase or decrease their biologic potency activity [4-6]. Therefore, attending to their pharmacological input to health, diverse synthetic flavones derivatives (e.g. nitro, amino, methoxylate) have been developed by several groups of chemical researchers in the last decades [4-10]. These compounds have displayed important biological effects such as chemo protective action against colon aberrant crypt foci in the rat colon (e.g. 3-nitroflavones series) [9], competitive and selective ligands for central benzodiazepine receptors and *in vivo* potent anxiolytic activity (e.g. 3-hydroxy-2'-methoxy-6-methylflavone) [6], anti-inflammatory (e.g. methoxylated chalcones) [4] and antimicrobial activities (e.g. 7,3`-dihydroxy-4´methoxyflavone) [10]. In my point of view, the most hopeful therapeutic activity is their selective anti-proliferative effects. Some of them are reported as *in vitro* potent antiproliferative agents against a panel of different human and murine tumor cell lines [4,5,8]. For example, Cardenas *et al.* [5] verified that synthetic 2`-nitroflavone significantly reduced the growth in 5 different tumor cell lines (i.e. cervix HeLa adenocarcinoma, oropharyngeal KB carcinoma, human cervical WISH carcinoma, breast MCF-7 cancer, F3II and LM3, both mammary adenocarcinoma). None of the tested compounds affected the proliferation of non-tumor epithelial cells, suggesting a selective effect against cultured tumor cells. In another study, Bandgar *et al.* [7] demonstrated that the introduction of a nitro group in the 3,4,5-trimethoxy chalcones completely inhibited the growth of human cancer cell lines (i.e. renal ACHN carcinoma, pancreatic Panc1 carcinoma, non small cell lung Calu1 carcinoma, non cell lung H460 carcinoma and colon HCT116 carcinoma) as compared to standard anticancer agents (flovopiridol and gemcitabine) and exhibited promising anti-inflammatory and antioxidant activities which seems to be beneficial for cancer treatment also. However, Liu and collaborators [8] reported that the use of nitro substituent to synthesize 6-isopropyl-3`-nitroflavone and 6-isopropyl-4`-nitroflavone inactivated the flavones antiproliferative effect against HepG-2 cells (i.e. a human hepatocellular carcinoma cell line), proving the significance of the structure-activity relationship. Additionally, a specific compound, 3`-methoxy-4`-nitroflavone, may act as an aryl hydrocarbon receptor agonist or antagonist of tumor cells based on its concentration and on the promoter context of particular gene [11].

A significant hurdle in the translation of these potential natural therapeutic candidates into the clinical domain lies is their inadequate delivery to the intended site of action. So, it is deemed to develop appropriate carriers for efficacy delivering the bioactives to their target (i.e. cells/tissues or organs). It is well known that the cellular delivery of compounds is affected by both the lack of selectivity of a number of compounds and the high restriction of transport therapeutic agents across cellular membranes [12]. In the topic of advanced drug delivery, various strategies can be adopted to improve the transport into the target site but nanoscale carries have been stimulated the burgeoning interest in the subject. Concerning the entrance of nanoparticles to the tissues structures, there are some approaches reported in the literature [13]. Therefore, one important mechanism is the passive delivery and targeting where the nanocarriers reach end points by the natural mechanisms, namely through enhanced permeability and retention effect [14]. For example, some organs present natural affinity for nanoparticles

Citation: Lopes CM. Lipid Colloidal Systems: A Strategy to Deliver Natural Bioactive Compounds. Austin Therapeutics. 2014;1(3): 2.

uptake (e.g. liver and spleen) mainly due to the absorption by reticuloendothelial system and pathological situations that present an enhanced vascular permeability like some tumors and inflammation-related diseases [15]. The active targeting through selective implies focused seeking out of the target, mostly through specific interaction of the surface targeting ligands on delivery system with receptors in the target site [16]. Among biomaterials-nanocarriers, those composed of lipids materials (e.g. liposomes and lipid nanoparticles) have unique properties, such as biocompatibility, biotolerability once they are composed by lipids similar to the physiological ones, which make them first-class excipients in formulations [17].

Liposomes have encountered some challenges, such as high *in vivo* instability, which results in fast drug release and short blood circulation half-life, and also limited physical stability during storage. Once many of synthetic bioactive of natural products are not water soluble, the use of lipid nanoparticles seems to be attractive approach to deliver them. Lipid nanoparticles are consider superior carriers which claimed to join the advantages of older and well-known other colloidal carriers (e.g. liposomes and polymeric nanoparticles) and to avoid some of their drawbacks, namely decrease the toxicity of cytotoxics and increase the expected bioactive`s *in vivo* half-life, mainly if nanoparticles are coated with hydrophilic polymer on their surface [18]. Lipid nanoparticles offer an economical and patient-friendly device to deliver drugs in various routes of administration (e.g. parenteral, oral, pulmonary, and intranasal) [19]. The direct visualization (gamma scintigraphy imaging) of nanocarriers-loaded bioactives in blood circulation and biodistribution following their administration to animals can play an essential role to screen the most promising activities and afterwards in clinical practices. Based on these considerations, further lipid nanoparticles could be functionalized with surface ligands to obtain defined biological response. In conclusion, the potential of biomaterials-nanocarriers as drug delivery systems is widespread nowadays, and so far it seems to be a smart idea.

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Austin Therapeutics - Volume 1 Issue 3 - 2014
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