NATURAL PRODUCTS LOADED IN NANOCARRIERS TO CROSS BIOLOGICAL BARRIERS

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Natural products (NPs) are fascinating molecules not exclusively for their exciting structure variability but also for their ability to interact with diverse targets. In spite of these advantages, in many cases, the impressive *in vitro* activity to less or not significant *in vivo* efficacy is generally due to drug poor water solubility, low lipophilicity and inappropriate molecular size resulting in reduced absorption due to difficulties to cross biological barriers. In the gastrointestinal tract, a variety of physiological and morphological barriers such as gastric pH, proteolytic enzymes, colonic microflora and mucus layer can severely affect NPs bioavailability. Skin is a further physiological barrier, which essentially consists of four layers, and the stratum corneous, the outer layer of the skin (nonviable epidermis) represents the rate-controlling barrier for diffusion for almost all compounds. Small lipophilic NPs such a mono- and sesquiterpens have high permeation properties and largely used as penetration enhancers, but they can also need of specific formulations because susceptible to volatilization and degradation, mainly by oxidation and isomerization. Other important barriers are the pulmonary and nasal mucosae where NPs bioavailability is often limited by rapid degradation and/or clearance by the mucociliary system and alveolar macrophages. Additionally, blood retinal barrier and blood-brain barrier (BBB) are among the most challenging, ensuring proper homeostasis, mainly due to very selective and restrictive bidirectional transport of endogenous and exogenous compounds. Absorption through each pathway is dependent on different physical characteristics, such as molecular weight, hydrophobicity, ionization constants, and stability of absorbing molecules as well as biological barriers. Different approaches can be used to increase barrier-crossing properties of NPs, based on chemical permeation enhancement using small lipophilic NPs, polysaccharides, dendrimers, cyclodextrins, and the design and production of appropriate drug delivery systems, in particular nanosized ones, which is the most attractive to enhance the permeation through paracellular, transcellular, carrier-mediated, and receptor-mediated transport. Some properties such as mucoadhesion and retention to the mucosa can also be used to increase the cross biological barriers to achieve optimal pharmacological action at pathological sites.

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Key words: *natural products, nanocarriers, crossing properties, enhanced stability, increased bioavailability*

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