Curcumin, from Indian spice to a molecular model in drug discovery?

Nature has provided a large variety of molecules, with different degrees of complexity and therapeutic applications. Curcumin (Fig. 1) is an example of such molecules. Curcumin is a natural compound isolated from the rhizomes of the plant *Curcuma longa* L. (known to provide the Indian spice, curry). Since the ancient times, curcumin has been used in traditional medicine throughout the orient for its healing and antioxidant properties. Nowadays, curcumin has been extensively studied and has proven to have several biological activities, such as: antimicrobial, antidiabetic, neuroprotective, antimalarial, and antitumor activities. Curcumin is also able to modulate multidrug resistance (MDR) in cancer, by inhibiting certain proteins that are responsible for the cellular efflux of antitumour drugs, thereby decreasing the intracellular drug concentration. Therefore, curcumin can also be seen like the “universal panacea”. From a clinical perspective, curcumin has two important drawbacks that limit its application: it is rapidly metabolized by the organism, and it is chemically unstable.

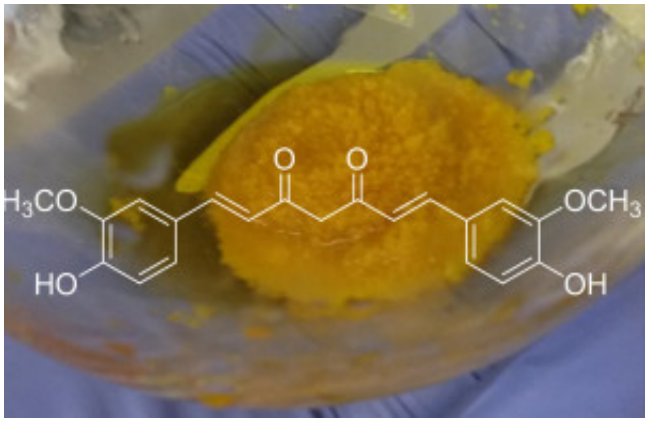

Fig. 1. Chemical structure of curcumin in a crude product of analogues’ synthesis.

Over the past few decades, thousands of molecules similar to curcumin (curcumin analogues) have been synthesized. Numerous strategies have been used to improve the stability, potency, and selectivity of these compounds. Regarding stability, the main strategies included the elimination of the reactive/unstable molecular portion of curcumin or the use of nanotechnology to protect the molecules from any undesirable chemical and/or biological environment.

Our work, “Curcumin: A Natural Lead for Potential New Drug Candidates”, aimed to review some of the strategies that have been developed to overcome curcumin’s chemical and biological limitations. This work has highlighted the synthesis and the molecular modifications introduced in curcumin analogues in order to potentiate certain biological activities, with special emphasis on

analogues to overcome MDR. In our perspective, curcumin can be considered a model for the development of drugs able to circumvent MDR. After thorough analyses of more than 200 curcumin derivatives, tractability in structure–activity relationship studies were found that suggest specific protein binding rather than membrane perturbations. It is likely that many years of research are still needed, involving cooperation among complementary fields of knowledge, to achieve a curcumin derivative that could be stable, potent and selective enough to be tested clinically.

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