NATURAL COMPOUNDS AS INHIBITORS OF LACTATE DEHYDROGENASE

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Lactate dehydrogenase (LDH) catalyses the conversion of pyruvate to lactate, utilizing NADH as co-factor. It's a tetrameric enzyme composed of two subunits, M and H, whose association can generate five isoforms. One of this, the human isoform 5, *h*LDH5 has the highest activity in converting pyruvate to lactate under anaerobic conditions, such as those found in hypoxic tumors and for this reason it's up-regulated in tumor tissues where cells glycolytic rate is up to 200 times higher than that of the normal tissue. *h*LDH5 inhibition should cause cancer cell death by starvation, without interfering with healthy cells that normally use oxidative phosphorylation for ATP generation (1). Inhibition of LDH is so considered as a promising target in cancer treatment, and natural compounds could serve as useful scaffold to study new anticancer agents. Among the few plant derived *h*LDH5 inhibitors already investigated there are mainly phenolic derivatives such as gossypol, morin, and galloflavin (2,3).

In the last decade our research group successfully detected a good number of compounds obtained from Mediterranean plants with anticancer effect, and for this reason start a research program aimed to discover new classes of natural products having *h*LDH5 inhibitory activity. In a first study, since some species of *Phlomis* (Lamiaceae) proved to possess anti-cancer properties, the crude extract of *P. kurdica* aerial parts was selected as the starting material. Two new flavonoids and one new phenylpropanoid, together with eleven known phenolic compounds, including flavonoids and phenylpropanoids were isolated and assayed for their *h*LDH5 inhibitory activity. Luteolin 7-*O*-β-d-glucopyranoside showed an IC_{50} value similar to that of

reference compound galloflavin (4). Then, since *Polygala* genus (Polygalaceae) is well known to contain phenolic oligosaccharides, xanthones, lignans, and triterpenic saponins and it's largely used in the traditional medicine, an Italian species *P. flavescens* subsp. *flavescens* was chosen. Ten new compounds were isolated from the methanol residue of the aerial parts through Sephadex and RP-HPLC separations, including four flavonol glycosides, two oligosaccharides, one α-ionone, and three triterpenoidic saponins, together with two known oligosaccharides and two flavonol glycosides. The isolates were assayed for their inhibitory activity against hLDH5 and 3,6'-di-*O*-sinapoylsucrose showed an inhibition potency comparable or even slightly better than reference inhibitor galloflavin. Docking studies were carried out to hypothesize the interaction mode of active compounds in the enzyme active site.

References

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