

Chemical modification of naturally occurring polyphenols for enhanced bioavailability and increased selectivity of their biological activity

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It is generally accepted view, that large number of plant secondary metabolites, particularly the phenylpropanoids of polyphenolic character abundant in edible plants, constitute non-nutritional but vital for health maintenance, elements of human diet. Scientific evidence for such thesis, which stems from epidemiological data and innumerable studies, conducted on molecular, cellular and *in vivo* models, has recently attained level of clinical trials, crucial for prospective medicinal applications.

Several classes of plant polyphenols are being studied (flavonols, catechins, isoflavones, lignans, coumarines, etc.) as antioxidants, detoxicants, chemoprotectants, phytoestrogens, immunomodulators, neuroprotecting compounds, antitumor agents, compounds restoring bones in osteoporosis, regulators of lipid metabolism and cardiovascular health promoters.

Although application of plant derived polyphenols in healthcare is already a booming business in poorly regulated dietary supplement, nutraceutical and cosmetic sectors, advances in new drug development based on these substances are still rather unimpressive. The main reasons for slow progress in pharmaceutical development are: difficulty in patent protection, lack of chemically pure natural polyphenols (active substances), their sub-optimal physicochemical properties, low bioavailability and unfavorable metabolism.

Focusing our attention on soy isoflavone: genistein, which is a drug candidate in at least two therapeutic categories: antitumor and hormone replacement therapy, we have demonstrated that the above mentioned drawbacks of plant derived polyphenols can be overcome with application of chemical synthesis and principles of medicinal chemistry. At first, we have developed technical process for genistein synthesis, securing availability of unlimited supply of the active substance of very high purity, for further pharmaceutical development. Secondly, research program for chemical derivatization of genistein and biological activity study of its new derivatives has been started, aimed at anticancer and anti-osteoporotic compounds, in order to exploit further pharmacophoric potential of the parent isoflavone. Our principal thesis, that modification of lipophilicity of the new genistein derivatives is crucial for their activity and/or selectivity profile, has already passed successfully the proof of principle point (*Cancer Letters* 2004 203:59-69).

We believe that our approach to new, patentable chemical entities (NCE) obtained by chemical modification of known natural polyphenols with aim of tuning up their biological activity, which we have demonstrated for genistein, is generally applicable to a wide selection of poly-hydroxylic natural products, such as: flavonoids, lignans, saponins, etc. With expertise in synthetic chemistry, pharmaceutical analysis and process development, executed under total quality control, according to current requirements of pharmaceutical development (Common Technical Document format), we offer reliable partnership for any program requiring supply of NCE samples, as well as pilot plant batches, for pre-clinical pharmacology, formulation development or clinical trials.