Chapter I. Justification and aims of the project

The present PhD project entitled “Phytochemical study of *Coreopsis tinctoria* and evaluation of its antidiabetic properties” resulted from the collaboration between the Medicinal Chemistry and Pharmacology Laboratories of Faculty of Pharmacy of University of Lisbon and both the Pharmaceutical Sciences Department and the Diabetes Research Group Laboratories of the School of Biomedical Sciences, King’s College London.

1.1. Justification the project

Diabetes mellitus is a metabolic disorder of high incidence. According to the World Health Organization, it is predicted that 366 million individuals worldwide will suffer from diabetes by 2030 (type 2 in 90% of the cases) (Wild et al., 2004). Morbidity and mortality of these patients is due to macrovascular and microvascular complications. The biochemical pathways leading to these pathologies are not well known but increased oxidative stress is widely accepted as a participant in the development and progression of diabetes and its complications (Maritim et al., 2003).

The risk of diabetes complications can be reduced with strict control of hyperglycemia but in many cases they cannot be avoided and have to be treated, increasing in more than 50% the costs of diabetes treatment (Bloomgarden et al 1999). Oral hypoglycemic drugs in the market are insulin secretagogues (sulphonylureas), insulin sensitizers (biguanides and thiazolidinediones), inhibitors of glucose absorption (alpha glucosidase inhibitors, guar-gum) and the recently introduced repaglinide and nateglinide, which are early-phase insulin secretagogues targeting post-prandial hyperglycemic peaks (Standl and Fuchtenbush 2003). None of these drugs act directly on the oxidative mechanisms leading to cardiovascular and neuropathologies associated with type 2 diabetes.

The search of new anti-diabetic drugs can be fully justified by the high incidence, increasing prevalence of type 2 diabetes, limitations, and side-effects of current hypoglycemic drugs. Those new antihyperglycemic drugs could be i) glucose absorption inhibitors acting on specific glucose transporters causing less drug incompatibilities than guar-gum, ii) glucose-sensitive insulin secretagogues avoiding the hypoglycemic effect of sulphonylureas, iii) orally active insulin mimetics avoiding the
inconvenience of insulin injections, and iv) insulin sensitizers acting on muscle and fat cells as well as on liver. Moreover, a drug combining hypoglycemic/antihyperglycemic activity with the capacity of inhibiting oxidative tissue damage would be ideal to control glycemia and prevent cardiovascular complications at the same time, decreasing therapeutic costs and inconvenience of multi-drug therapies.

Several plant extracts have been claimed to have hypoglycemic activity but toxicities of those extracts, active principles and mechanisms of action are generally not well known (Yeh et al., 2003). Among the natural products identified as hypoglycemic agents there is a yellow pigment (phlorizin). Phlorizin, a natural monoglucoside flavonoid, is known to produce glycosuria and block intestinal glucose absorption through competitive inhibition of sodium-dependent glucose transporter (Ehrenkranz et al., 2005), which could be of some importance in the management of postprandial hyperglycemia, but it lacks antioxidant properties.

Coreopsis tinctoria Nutt. is used traditionally in Portugal as a hypoglycemic agent and although further pharmacotoxicological and phytochemical studies are needed, it is known to contain metabolites structurally related to phlorizin (Crawford et al., 1983; Harborne, 1977), which supports the need of further investigation on the chemical composition and antidiabetic profile of this already commercialized herbal drug.

1.2. Aims of the project

Considering the above mentioned state of the art, the main aims of this project are:

i) To search for new antidiabetic lead molecules, able to reduce both glycemia and oxidative tissue damage;

ii) To chemically characterize the bioactive extracts of C. tinctoria.

iii) To study the antidiabetic profile of extracts and metabolites of C. tinctoria.

Overall, this project is also expected to contribute to public health through clarification on the efficacy and the development of analytical methods to assure quality of this commercialized herbal drug.