**2. Dissertation hypothesis, motivation and goals**

**2.1 Hypothesis**

Glucose transporters (GLUTs) family, GLUT 1 to 14, are responsible for the entrance of glucose into cells. Muscle, hepatic and adipose cells selectively increase their glucose uptake in response to insulin. In these tissues, GLUT4 is the predominant glucose transporter, distinguished by its continuous cycling between the plasma membrane and intracellular stores. Modulations of the cycling rate result in different steady-state distributions that determine net glucose influx. Skeletal muscle is the major tissue absorbing circulating glucose during a meal. In T2DM, insulin resistance, particularly in skeletal muscle, is associated with insufficient recruitment of GLUT4 to the cell surface in the face of normal GLUT4 expression and elevated insulin. Hence, enhancing GLUT4 translocation to the PM by medicinal plants will be a key for the design of appropriate strategies to resolve insulin resistance. We will use skeletal muscle cell line (L6) stably expressing myc-tagged GLUT4 as an in-vitro model to asses GLUT4 translocation to the PM. The myc epitope on the exofacial loop of GLUT4 allow us to quantitatively assess the relative amount of GLUT4-myc in the PM in response to insulin and other stimuli.

**2.2 Dissertation motivation and goals**

During the last two decades, traditional systems of medicine and medicinal plant research have become topics of global interest and importance. Plant natural products have a long tradition as important starting points for medicinal chemistry and drug discovery. Recently, there has been a renewal of interest in the involvement of these products in compound collections for screening and achieving selective target modulation.

Some of the most popular anti-diabetic drugs have been obtained from plants, such as galegine (isolated from *Galega officinalis*, which has a great resemblance to the antidiabetic drug metformin), picnogenol, acarbose, miglitol and other antidiabetic products. Despite the relatively large number of existing anti-diabetic drugs, still there are patients whom therapy resistant. Moreover, all the existing drugs have side effects that disturb patient's life and in some cases these side effects could lead to serious damages, including deaths from hepatic failure. Thus, there is an unmet need to develop new anti-diabetic drug, this leading us to the main purpose of this PhD thesis, which is to discover new lead compound(s)/fraction(s) from medicinal plants for future drug development.

The specific aims of the PhD work are:

* + 1. Selecting twelve medicinal plants, according to reports of local alternative medicine practitioners on effective anti-diabetic medicinal plants, that were not tested before for GLUT4 translocation and activity.
    2. Preparing different medicinal plant extracts using several extraction techniques, for choosing the ultimate extract for further testing.
    3. Testing the toxicity of the plant extracts using MTT and LDH leakage assays, for choosing the safe concentration of the prepared extracts, for further testing.
    4. Testing the anti-diabetic activity for all plant extracts, by using the muscle cell line L6GLUT4myc, for measuring the GLUT4 translocation to the PM.
    5. Testing the chemical composition of all prepared organic extracts to obtain chemical profile for the plant extracts, using the GCMS method.
    6. Focusing on one plant extract (MeOH GT extract) for further analyzing, fractionation, cytotoxicity, GLUT4 translocation and chemical profile for all fractions.