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Full Length Research Paper

Acute and chronic hypoglycaemic effect of Achillea santolina aqueous leaves extract

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Achillea santolina, (Asteraceae) is a plant traditionally used in Iraq, Egypt and Pakistan as a tonic, vermifugal and carminative and also for stomach pain and hypertension. It contains several polyphenols, a family of compounds with a great anti-diabetic potential. The present study investigates the hypoglycemic effect produced by the acute and chronic administration of Achillea santolina leaf extract in streptozotocin (STZ)-induced diabetic rats. Oral glucose tolerance tests (OGTT) were conducted in STZ-diabetic rats using orally administered glucose (5 g/kg body weight) followed or accompanied by the leaf extract (150 or 250 mg/kg body weight). Weekly plasma glucose concentrations were recorded in control STZ-diabetic rats and diabetic rats orally treated with the leaf extract. The acute administration of the aqueous extract of A. santolina resulted in significant reductions of glycemia in diabetic rats after oral administration at doses of 250 mg/kg and 150 mg/kg. Since the A. santolina extract showed a marked hypoglycemic activity, it was administered daily *per os* to streptozotocin diabetic rats during 28 days. After 28 days of A. santolina extract administration at a dose of 250 mg/kg/day, diabetic rats showed improvement in glycemia when compared with the diabetic control group. In conclusion our results demonstrate that A. santolina seems to present some interesting hypoglycemiant effects with a drug dose dependant response.

Key words: Anchilea, santolina, diabetes Mellitus, HOMA, glucose, insulin.

INTRODUCTION

Diabetes mellitus is a complex metabolic disorder that affects between 6 to 20% of the population in Western industrialized societies, with an estimated worldwide prevalence of 150 million people in 2000, a number that is expected to increase to 220million people in 2010 (Zimmet et al., 2001; Fracchiolla et al., 2007). Furthermore, taking into account its present rate of increase, within few decades it will be one of the world's commonest diseases and one of the biggest public-health problems with an estimated minimum of half-a-billion cases (Diamond, 2003).

Up to now, many kinds of antidiabetic medicines have been developed for the patients and most of them are chemical or biochemical agents aiming at controlling or/and lowering blood glucose to a normal level.

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Plant materials which are used as traditional medicine for the treatment of diabetes are considered some of the finest sources for the development of new drugs. Plant extracts or plant preparations are being prescribed by the traditional practitioners and also accepted by the users for diabetes in many countries.

Despite the impressive advances in health sciences and medical care, there are many patients who are still using complementary or alternative therapies alone to the prescribed medication. Traditional plant remedies or herbal formulations exist from ancient times and are still widely used despite all the controversiesassociated with their efficacy and safety (Huxtable 1990;Fugh-Berman 2000),Very few plants widely used in folk medicine, are still tested and screened for their pharmacological activities. Yet they provide an unlimited source of big interest compound which can further become new active drugs. Recently, there has been renewed interest in the

use of plant compounds as antidiabetic compounds (Pari and Saravanan, 2002), and more than 1200 plant species have been found to exhibit antidiabetic properties (Jouad et al., 2000; Jouad et al., 2002a and Jouad et al., 2002b; Eddouks et al., 2003). Furthermore the WHO expert committee (1985) recommended scientific investigation of hypoglycaemic agents of plant origin for the treatment of diabetes mellitus.

Most of the studies concerning Achillea gender, which belongs to the Asteraceae (also named Compositeae) family, report antibacterial and antifungal activities.

Achillea santolina L. an herb, which belongs to the Asteraceae family, grows in Iraq, Egypt, Baluchistan and the North West frontier province of Pakistan. In folk medicine, it is widely used as a tonic, vermifugal and carminative, and also used for stomach pain and hypertension. Hatam et al, (1988) had shown that A. santolina possesses some antimicrobial activity. The aerial parts are used to cure stomach ache in children (Kirtikar et al, 1975), its carminative effect and for dysentery and abdominal pain (Chakravarty, 1976).

Chemical analysis revealed that A. santolina contains flavones, particularly flavonoids and sesquiterpene lactone (Hatam et al, 1988), and polyphenols have been reported to have some beneficial antidiabetic effects (Sabu et al., 2002; Al Awwadi et al., 2004).

The aim of the study was therefore to assess the antidiabetic effect of A. santolina in streptozotocin induced diabetic rats which is considered as a valuable tool for the pathophysiology and pharmacology studies of type 1 diabetes mellitus (Burcelin et al., 1992 and Burcelin et al., 1995).

MATERIAL AND METHODS

Plant Extract

A. santolina was collected in Iraq and dried at room temperature. The aerial parts of A. santolina, essentially dried leaves, were powdered and infused in boiling water. After cooling, the resultant decoction was then filtered and lyophilised.

Animals

Experiments were performed on male Wistar rats weighing 200-220 g from Iffa Credo (Labresle, France). The rats were housed in an environmentally (temperature and humidity) controlled room with a 12h- light:12-h dark cycle, and had free access to standard rat chow and tap water. After an adaptation period of one week, rats were randomly divided into three groups of five rats each.

Induction of experimental diabetes

Diabetes was induced by a single injection of sreptozotocin (STZ, 60 mg/kg, i.v.), in the tail vein, and the diabetic state (glycaemia >2 g/l) checked 72h after the injection by evaluation of fasting glycaemia on blood from a cut to the tail using an Ames Glucometer.

Experimental design

Oral glucose tolerance test

The hypoglycemic effect of aqueous extract of A. santolina leaves in diabetic rats was assessed by improvement of glucose tolerance.

After an overnight fasting, rats of all the groups were given glucose (5 g/kg), and 30 min after control rats received by gavage water whereas two doses of 150 and 250 mg/kg of leaf extract were administered to the other two groups. Blood samples from the tail vein were collected just prior to glucose administration (0 h) and 1, 2, 3 and 4 h after glucose loading and blood glucose levels were measured by an Ames Glucometer

Long term studies

Rats were daily treated by gavages for 4 weeks, one group at the dose of 250 mg/kg and the other with 150 mg/kg. The drug solutions or vehicle were administered orally by gastric intubation using a syringe once daily in the morning.

Plasma glucose level was measured during all the study by a weekly measure, before administration of the extract, and after two weeks of treatment a glycaemia control study was assessed by measuring glycaemia evolution during six hours after the administration of the extract.

At the end of the treatment an OGTT was done after the administration of the extract (T0) and those of glucose (T0).

To test the intestinal inhibition of carbohydrates absorption property of the extract, an intraperitoneal glucose tolerance test (IPGTT) was done at doses of 250 and 150 mg/kg, where the rats were given the extract and the glucose simultaneously.

Statistical analysis

Data were expressed as mean +/- SEM. Statistical differences were assessed using the ANOVA followed by Student –Newman Keuls post-hoc test. The level of significance was set to $P< 0.05$.

RESULTS

Single oral administration

The effects of a single oral administration of A. santolina at doses of 150 mg/kg or 250 mg/kg in STZ diabetic rats

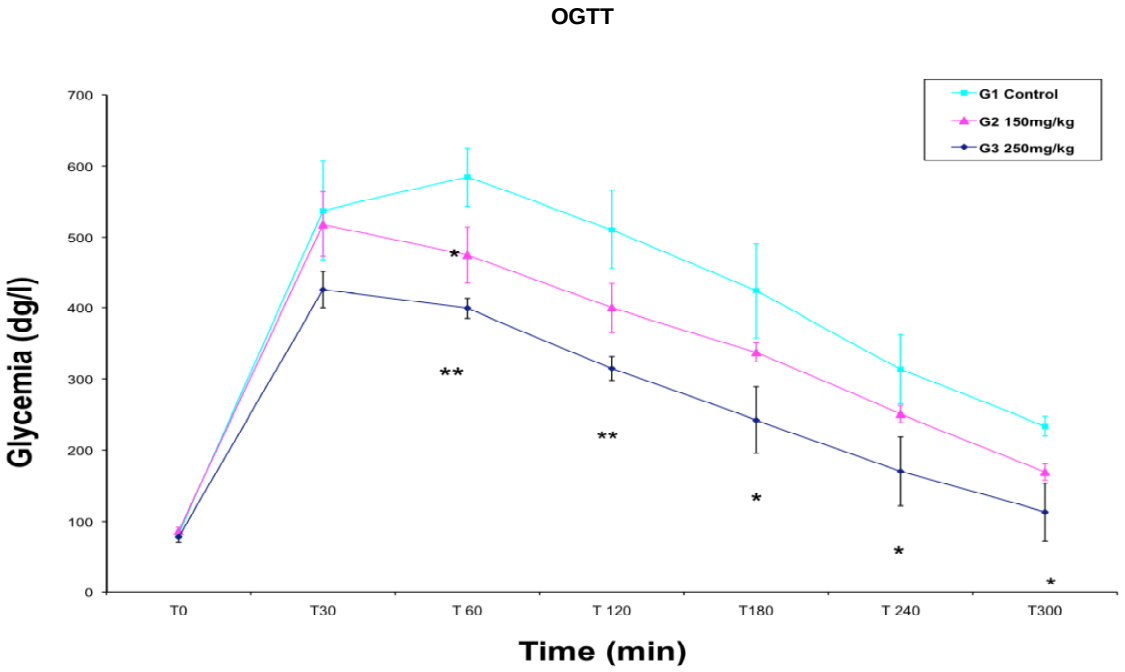


Figure 1: Effect of oral administration of 250 mg/kg and 150 mg/kg of A. santolina aqueous extract (T30) on plasma glucose level (dg/L) of oral glucose loaded (T0) streptozotocin rats. Values are means ± S.E.M. *P<0.05; **P<0.01; ***P<0.001 vs. control (n=5 per group).

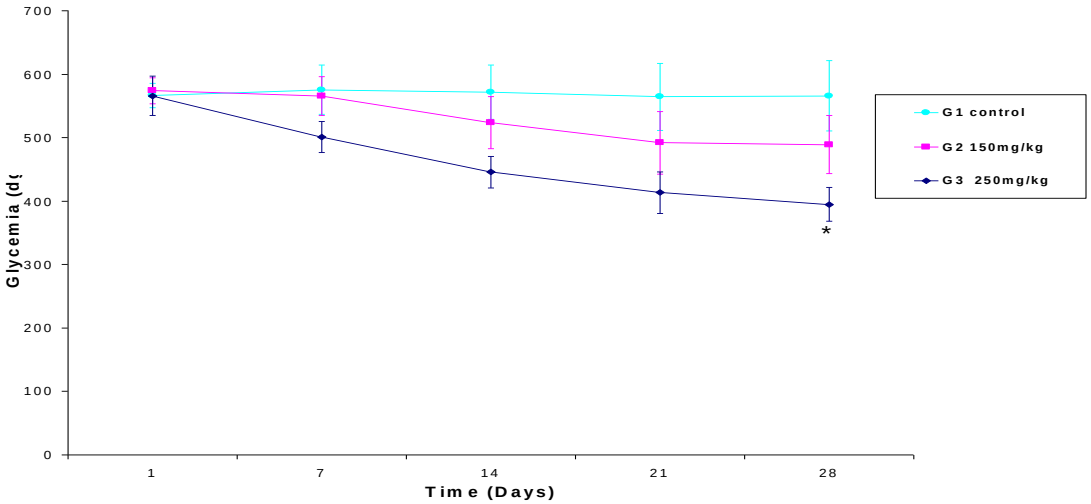


Figure 2: Evolution of plasma glucose levels (dg/L) after once daily repeated oral administration of aqueous A. santolina extract (250 mg/kg and 150 mg/kg) for 28 days in streptozotocin induced diabetic rats. Values are means ± S.E.M. *P<0.05; **P<0.01; ***P<0.001 vs. control (n=5 per group).

on glucose tolerance test are shown in Figure.1. The blood-glucose concentrations of the control diabetic rats reached a peak of 30-60 min after the oral administration of 5 gm glucose had gradually decreased. The dose of 250 mg/kg when compared to the control group induced a significant decrease in the blood-glucose concentration from 60 min to 300 min, whereas the dose of 150 mg/kg only reduced blood glucose level at 60 min.

Repeated oral administration

The effects on blood glucose levels of once daily repeated oral administration of A. santolina (250 and 150 mg/kg/day) in STZ diabetic rats are shown in Figure.2. In

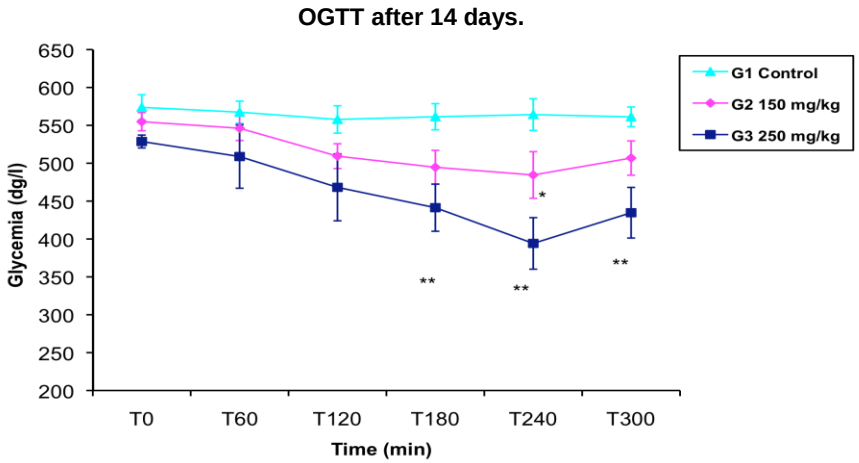


Figure 3: Effect of oral administration of 250 mg/kg and 150 mg/kg of A. santolina aqueous extract (T0) on plasma glucose level (dg/L) of streptozotocin rats after 14 days of treatment. Evolution of BG recorded after an OGTT Rats were fasted for 12 h and untreated before glucose (5 g/kg) oral administration. Treatment induced significant change in animals. Treated groups BG was significant Values are means ± S.E.M. *P<0.05; **P<0.01; ***P<0.001 vs. control (n=5 per group).

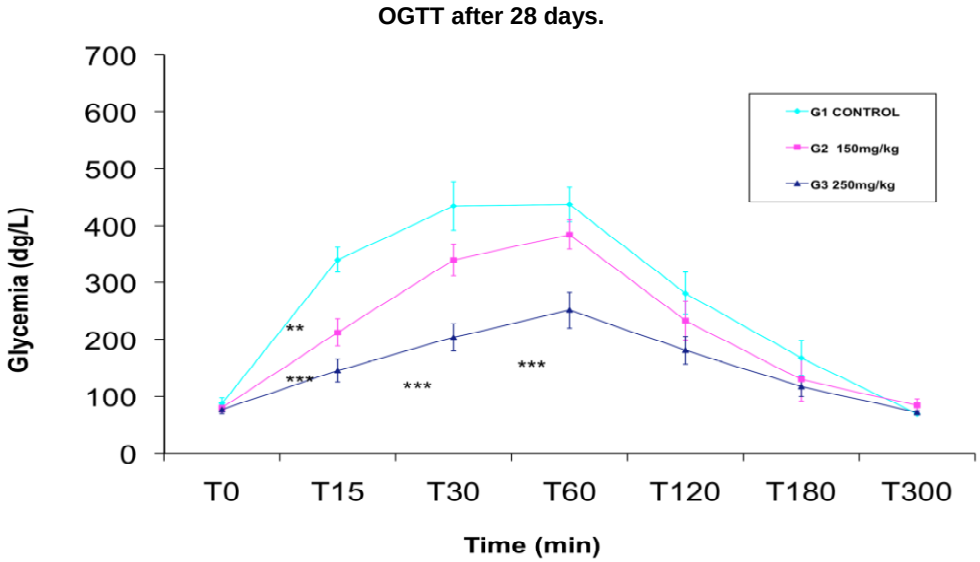
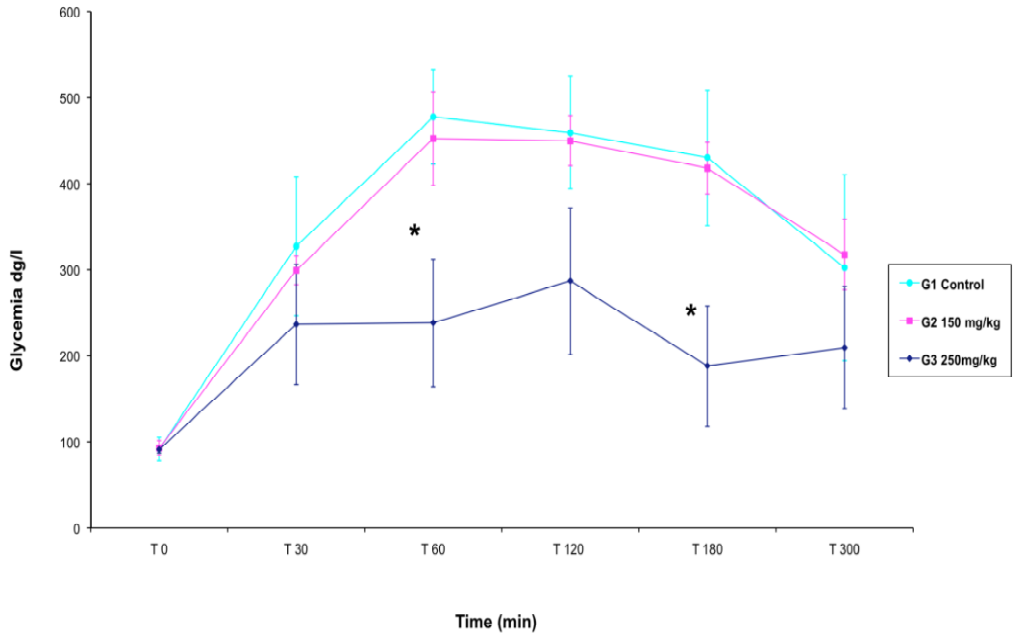


Figure 4: Evolutionof BG recorded after an OGTT Rats were fasted for 12 h and untreated before glucose (5 g/kg) oral administration. Effect of oral administration of 250 mg/kg and 150 mg/kg of A. santolina aqueous extract (T0) on plasma glucose level (dg/L) of oral glucose loaded (T0) streptozotocin rats after 28 days of treatment. Treatment induced significant change in BG of animals treated groups. Values are means ± S.E.M. *P<0.05; **P<0.01; ***P<0.001 vs. control (n=5 per group).

control rats, the blood glucose levels did not change. By contrast, two, three, and four weeks after the start of A. santolina treatment at doses of 150 mg/kg or 250 mg/kg, blood glucose levels showed a slight decrease, and this decrease became significant decrease for the dose of 250mg/kg after 4 weeks of treatment (P < 0.05).

In Figure.3 the results illustrates the evolution of the glycemia level made after two weeks of treatment in the two treated groups respectively treated with 250 mg and 150 mg of A. santolina extract, compared to the control group. The treatment with the highest dose of extract (250mg) significantly decreased glycemia 180, 240 and 300 min after the administration of the extract, whereas the lower dose (150 mg/kg) only reduced glycemia 240 min after the administration.

The results of OGTT after 28 days of treatment**.** Represented by the Figure.4, which showed the evolution of the glycaemia level during an oral glucose tolerance test (OGTT) made after 4 weeks of treatment.



IPGTT

Figure 5: Evolutionof BG recorded after an IPGTT Rats were fasted for 12 h and untreated before glucose (5 g/kg) oral administration Effect of oral administration of 250 mg/kg and 150 mg/kg of A. santolina aqueous extract (T0) on plasma glucose level (dg/L) of intra-peritoneal glucose loaded (T0) streptozotocin rats after 28 days of treatment. Values are means ± S.E.M. **P*<0.05; ***P*<0.01; ****P*<0.001 vs. control (*n*=5 per group).

This results showed significant differences from 15 min to 60 min for the highest dose (250 mg/kg) in ($p<0.001$) and at 15 min only for the lower dose ($p<0.01$).

Figure. 5 illustrates an intra-peritoneal glucose tolerance test (IPGTT) made after 4 weeks of treatment, to test the intestinal inhibition of carbohydrates absorption property of the extract. Only the highest dose of the extract (250 mg/kg) decreased blood glucose level significantly at 60 min and 180 min after the administration ($p<0.05$). But there is no significant change in BG produced by the treatment by 150 mg/kg.

DISCUSSION

A. santolina is a traditional medicinal plant whose main pharmacological activities have been shown to be antibacterial, vermifugal and carminative, but no studies have been done on diabetic status. We therefore studied the anti-diabetic effect of an acute or a chronic administration of A. santolina in streptozotocin induced diabetic rats.

First, to study the acute hypoglycaemic effect of aqueous extract of A. santolina leaves in diabetic rats, the extract was administrated 30 min after the glucose solution in an OGTT. A single oral administration of A. santolina (250 mg/kg) induced a significant and long term decrease of the glycaemia, after the absorption of the glucose. A. santolina has therefore acute peripheral effects, may be on carbohydrate metabolism, or by helping the clearance of the glucose.

We then studied the effect on glucose blood level of a chronic administration, and we observed a progressive decrease becoming significant with the highest dose, after 4 weeks of treatment.

The anti-hyperglycaemic chronic effect of A. santolina is therefore progressive and accumulative.

After two weeks of treatment, the measurement of the glycemia evolution after treatment showed a delayed and transitory effect.

After the end of the treatment, the OGTT revealed a marked, but early and transitory effect, of A. santolina. We must notice that the extract and the glucose were co-administrated, so as to evaluate the effect of the extract on glucose absorption. Indeed, the hypoglycaemic activity of the plant may partly be due to the inhibition of carbohydrates absorption because no significant hypoglycemic effect was seen when the low dose of extract was intra-peritonealy administrated. However, the highest dose had a transient hypoglycemic activity in the IPGTT.

The present results demonstrated that the aqueous extracts of A. santolina exerted have a significant and potent anti-hyperglycaemic activity in STZ-diabetic rats, an experimental model of type 1 diabetes mellitus

(Burcelin et al., 1995). The high dose used (250 mg/kg) and the duration of treatments (four weeks) improved glucose tolerance in severely diabetic rats with fasting glycemia. After repeated oral administration, A. santolina presented a glucose lowering activity.

These effects may partly results from a central and/or peripheral activity, and partly from the inhibition of carbohydrates absorption.

Moreover flavonoids have been shown to influence glycemia through inhibition of several digestive enzymes (Longstaff and McNab, 1991), like amylase (Thompson et al., 1984) thereby inhibiting lipids or carbohydrates digestion, and post-prandial glycemia.

In previous study we showed that a red wine polyphenol extract, ethanol, or their association have some antidiabetic activity on a model of diabetes linked to insulin deficiency, the STZ-induced diabetic rat, characterized by a major hypergly- cemia (Al awwadi et al., 2004).

On the other hand, A. santolina could influence insulin receptor by a peripheric effect on liver, muscle or adipose tissue or by a central effect on beta-cell, with an insulino-secretory effect. In conclusion, the aqueous extracts of A. santolina have potent anti-hyperglycaemic effects in STZ diabetic rats. Further studies are necessary to determine the precise action mode of the compounds of this acqueous extract of A. santolina.

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