International Scholars Journals

International Journal of Medicinal Plants Research ISSN 2169-303X Vol. 4 (7), pp. 151-156, September, 2013. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Anti diabetics effect of *Achillea santolina* aqueous leaves extract

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Accepted 30 June, 2015

Achillea santolina, (Asteraceae) a plant traditionally used in Iraq, Egypt and Pakistan as antidiabetic, anti-inflammatory and to relieve pain. Also as a tonic, vermifugal and carminative, and also for stomach pain and hypertension, 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 in comparison 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: Achilea , Santolina, diabetes mellitus, HOMA, glucose, Insulin.

INTRODUCTION

Plants have been used as drugs by humans since thousands of years ago. 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 compounds which can further become new active drugs. Recently, there has been renewed interest in the use of plant compounds as antidiabetic compounds (Al-Awwadi N.,et al (2004), and more than 1200 plant species have been found to exhibit antidiabetic properties (Krosniak,M.,etal 2004)' (Burcelin R., et al 1992, 1995)' (Furthermore the WHO expert committee (1985) recommended scientific investigation of hypoglycaemic agents of plant origin for the treatment of diabetes mellitus (Chakravarty HL (1976).

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 Irak, Egypt and in 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. (Eddouks M., et al, 2003) had shown that A. santolina possesses some antimicrobial activity. The aerial parts are used to cure stomach ache in children' (Hatam NAR. et al 1988), its carminative effect

and for dysentery and abdominal pain. (Jouad H, et al 2000)
Chemical analysis revealed that A. santolina contains flavones, particularly flavonoids and sesquiterpene Lactone (Eddouks M. et al 2003), and polyphenols have been reported to have some beneficial antidiabetic effects. .
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. (Longstaff M, et al 1991),(Pari L, Saravanan G (2002) .

MATERIAL AND METHODS

Plant Extract

A. santolina was collected in Irak 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 a 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 vain 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 gavage 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 glycemic control study was assessed by measuring glycemia 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 on glucose tolerance are shown in Figure 1. The blood-glucose concentrations of the control diabetic rats reached a peak 30-60 min after the oral administration of glucose and 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 control rats, the blood glucose levels did not change. By contrast, two, three, and four weeks after the start of A.

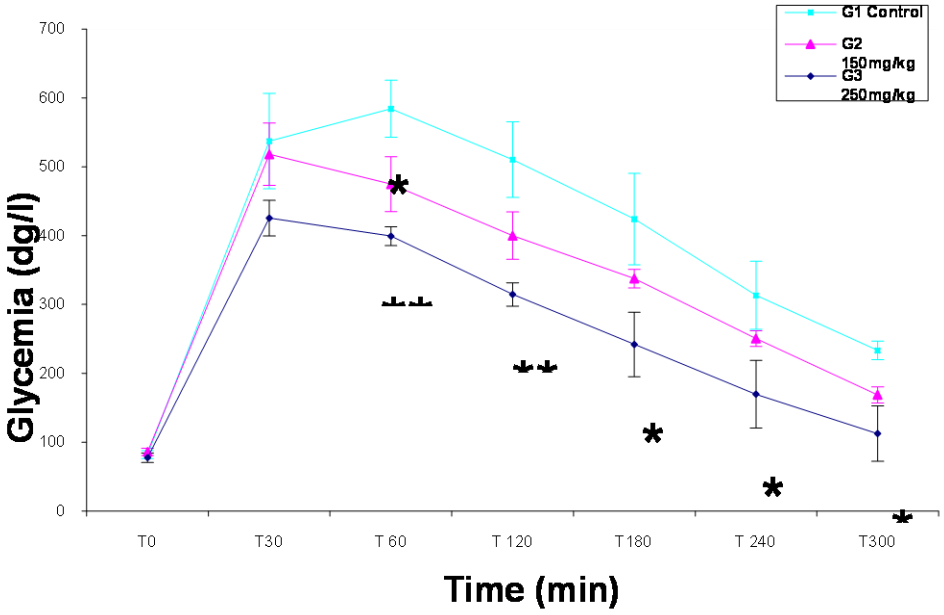


Figure 1. Effect of oral administration of 250 mg/kg and 150 mg/kg of A. santolina aqueous extract (T30) on plasma glucose level (dg/L) of oral glucose loaded (T0) streptozotocin rats. Values are means ± S.E.M. **P*<0.05; ***P*<0.01; ****P*<0.001 vs. control (*n*=5 per group).

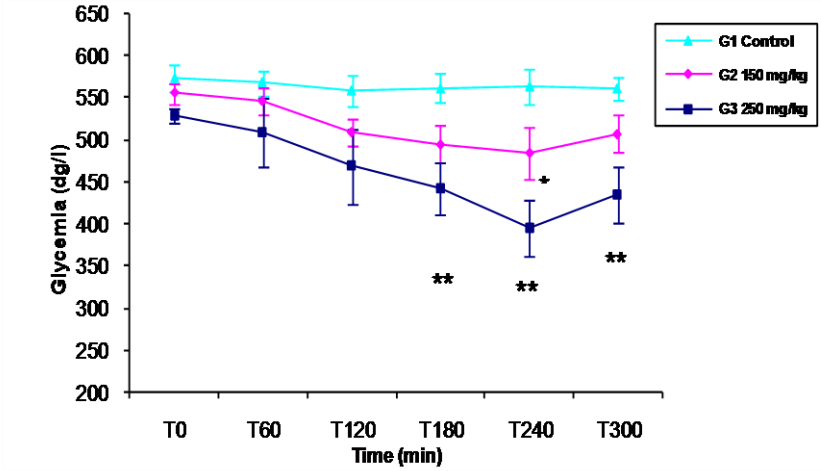


Figure 2. Evolution of plasma glucose levels (dg/L) after once daily repeated oral administration of aqueous A. santolina extract (250 mg/kg and 150 mg/kg) for 28 days in streptozotocin induced diabetic rats. Values are means ± S.E.M. **P*<0.05; ***P*<0.01; ****P*<0.001 vs. control (*n*=5 per group).

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 ($P < 0.05$).

Figure 3 shows 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.

Figure 4 represents the evolution of the glycemia level during an oral glucose tolerance test made after 4 weeks of treatment. The results showed significant differences

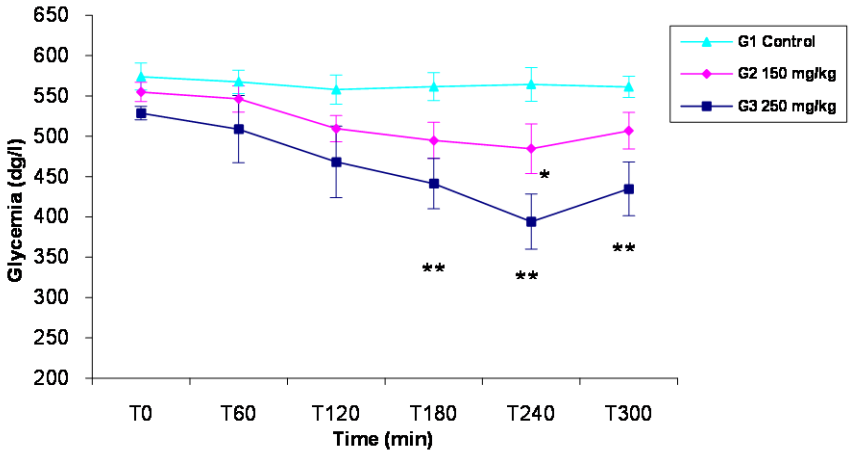
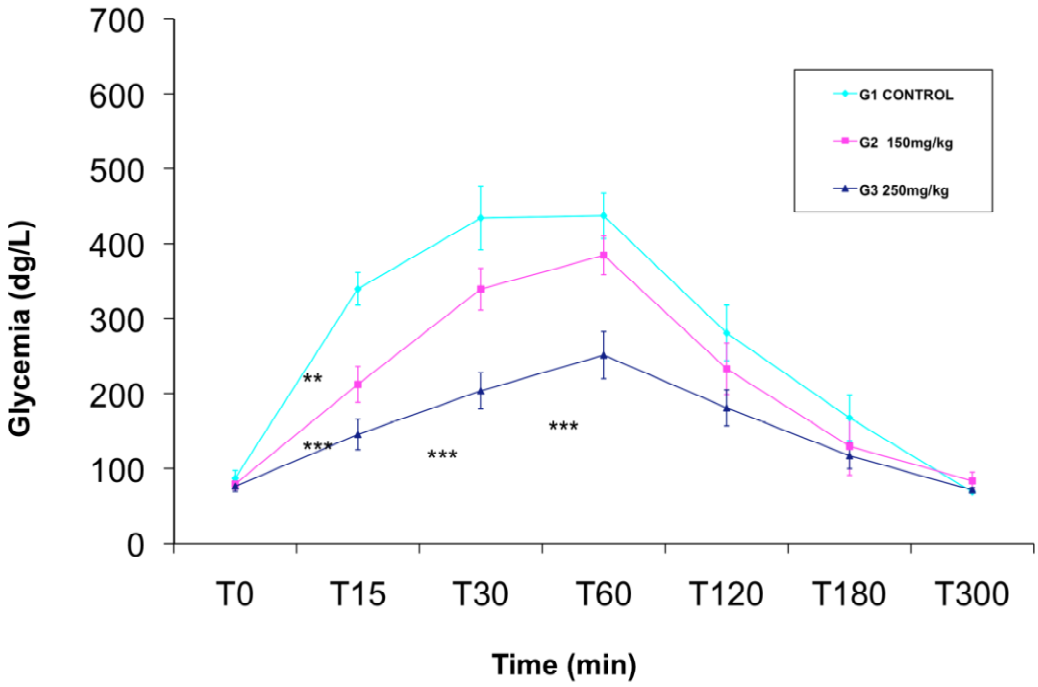


Figure 3. OGTT after 14 days.

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. Values are means ± S.E.M. *P<0.05; **P<0.01; ***P<0.001 vs. control (n=5 per group).



OGTT after 28 days.

Figure 4. 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. Values are means ± S.E.M. *P<0.05; **P<0.01; ***P<0.001 vs. control (n=5 per group).

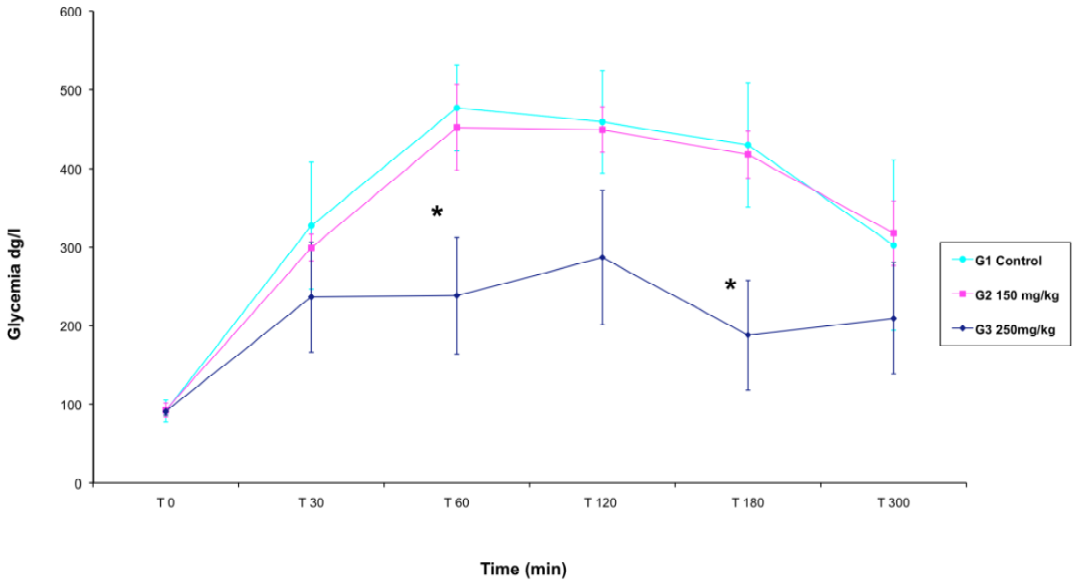


Figure 5. Effect of oral administration of 250 mg/kg and 150 mg/kg of A. santolina aqueous extract (T0) on plasma glucose level (dg/L) of intra-peritoneal glucose loaded (T0) streptozotocin rats after 28 days of treatment. Values are means ± S.E.M. *P<0.05; **P<0.01; ***P<0.001 vs. control (n=5 per group).

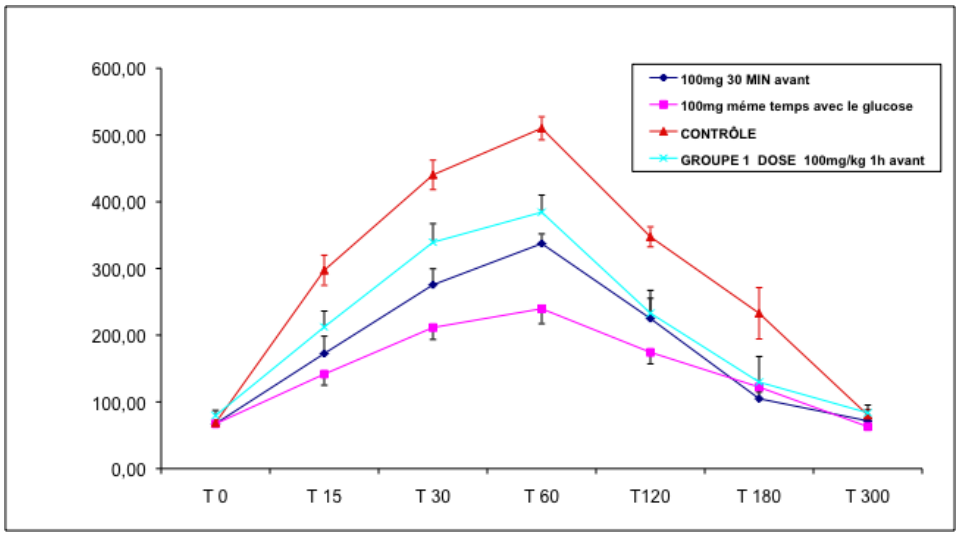


Figure 6. Effect of oral administration of 250 mg/kg and 150 mg/kg of A. santolina aqueous extract (T0) ,(T30 and T60) befor on plasma glucose level (dg/L) of oral glucose loaded (T0) streptozotocin rats after 28 days of treatment. Values are means ± S.E.M. *P<0.05; **P<0.01; ***P <0.001 vs. control (n=5 per group).

from 15 min to 60 min for the highest dose (p<0.001) and at 15 min for the lower dose (p<0.01).

Figure 5 illustrates an intra-peritoneal glucose tolerance test 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 decreased blood glucose level 60 min and 180 min after the administration (p<0.05).

DISCUSSION

In our study we proved that an acute administration of the

aqueous extract of Achillea santolina (in a dose of 150 and 250 mg/kg body weight orally) resulted in significant reductions of serum glucose level in streptozotocin -induced diabetic rats. Chronic administration of the aqueous extract of Achillea santolina in a dose of 250 mg /kg orally for 28 days also showed marked hypoglycemic effects in streptozotocin -induced diabetic rats in comparison with diabetic control group this results are in agreement with (Jouad H. et al 2002),(Kirtikar KR, et al 1975). This results also approved by (Khan MA. 1998) he found that the dried aerial parts and flowers of the plant were used traditionally as antidiabetic and as anti-inflammatory also Ardestani A. et al (2006) found that the elevated levels of liver malondialdehyde and protein carbonyls were significantly reduced in diabetic rats fed the extract. In addition, the decreased levels of antioxidant enzyme (SOD and CAT) and glutathione were significantly improved with the extract. Achillea santolina extract decreased serum glucose level and modulated serum ALP (alkaline phosphatase), ALT (alanine transaminase), and AST (aspartate transaminase) in streptozotocin -induced diabetic rats A. santolina is a traditional medicinal plant which main pharmacological activities have been shown to be antibacterial, vermifugal and carminative,. We therefore studied the antidiabetic effect of an acute or a chronic administration of A. santolina in streptozotocin induced diabetic rats.

First, to study the acute hypoglycemic 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 glycemia, 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-hyperglycemic 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-peritoneal 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 a significant and potent anti-hyperglycaemic activity in STZ-diabetic rats, an experimental model of type 1 diabetes mellitus (Pari L, Saravanan G (2002). 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.(Sabu MC, et al 2002)' like amylase (Thompson LU, et al1984) thereby inhibiting lipids or carbohydrates digestion, and post-prandial glycemia.

On the other hand, A. santolina could influence insulin receptor by a peripheric effect on liver, musle or adipose tissue or by a central effect on beta-cell, with a insulino-secretory effect may be attributed to protective or anti oxidative effect of achilea s. extract on lipid peroxidation, protein oxidation and antioxidant defense system (superoxide dismutase (SOD), catalase(CAT) and reduced glutathione) in the liver of streptozotocin -induced diabetic rats.(Ardestani A. et al (2006) (2007).

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 mode of action of the compounds of this acqueous extract of A. santolina.

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