**The English Summary – Ph.D. Thesis**

# Pharmacological study of the possible interactions between certain antidiabetics and selected antiepileptic drug in experimental animals

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# SUMMARY AND CONCLUSIONS

In the present study, both in vivo and in vitro experiments were carried out in order to study the possible interactions between certain antidiabetics and selected antiepileptic agent in experimental animals.

The purpose of the in vitro experiments was to investigate the possible effects of gliclazide (10, 20, 40 µmol/l), aqueous extract of *Morus alba* leaves ( 10, 20, 40 µg/ml) , aqueous extract of ginseng radix ( 25, 50, 100 µg/ml) and carbamazepine ( 10, 20, 40 µmol/l), alone and in combination on basal ( glucose 3 mmol/l) and glucose 16.7 mmol/l - stimulated insulin secretion using isolated rat pancreatic islets technique.

The purpose of the in vivo experiments was to investigate the possible effects of gliclazide (10 mg/kg), carbamazepine (50 mg/kg), aqueous extract of *Morus alba* leaves (100 mg/kg) and aqueous extract of ginseng radix (100 mg/kg) alone and in combination in streptozotocin ( 50 mg/kg)- induced diabetic rats. The effects of these treatments on serum glucose and insulin levels were investigated after two weeks of daily dose administration. The effects on serum glucose and insulin levels and insulinogenic index during oral glucose tolerance test were also studied after two weeks of daily dose administration.

The effects of the aforementioned treatments on liver glycogen content and blood MDA, nitric oxide and GSH were also investigated.

**The main findings of the present study can be summarized as follows:**

- **In vitro study:**

1. Glucose (16.7 mmol/l) significantly increased insulin secretion from isolated pancreatic islets.

2. Gliclazide (10µmol/l) has no effect on both basal and stimulated – insulin secretion. On the other hand, gliclazide (20, 40 µmol/l) increased both basal and stimulated- insulin secretion from isolated pancreatic islets.
3. Carbamazepine (10, 20, 40 µmol/l) did not significantly affect both basal and stimulated – insulin secretion from isolated pancreatic islets.
4. *Morus alba* (10 µg/ml) and ginseng (25µg/ml) have no effects on basal or stimulated- insulin secretion .On the other hand, *Morus alba* (20, 40 µg/ml) and ginseng (50, 100 µg/ml) significantly raised basal and stimulated - insulin secretion from isolated pancreatic islets.
5. Combination of gliclazide (10 µmol/l) and carbamazepine (10 µmol/l) did not significantly alter basal and stimulated-insulin secretion. Combination of gliclazide (20, 40 µmol/l) carbamazepine (20,40 µmol/l) significantly raised basal and stimulated-insulin secretion but this effect was not significant from gliclazide alone.
6. Combination of *Morus alba* ( 10 µg/ml) and carbamazepine (10 µmol/l) had no effect on both basal and stimulated-insulin secretion .On the other hand, combination of *Morus alba* (20,40 µg/ml) and carbamazepine (20,40 µmol/l) significantly increased both basal and stimulated -insulin secretion from isolated rat pancreatic islets. There is no interaction between *Morus alba* and carbamazepine when administered together.
7. Combination of ginseng (25 µg/ml) and carbamazepine (10 µmol/l) had no effect on basal insulin secretion .On the other hand, combination of ginseng (50,100 µg/ml) and carbamazepine (20, 40

μmol/l) significantly increased basal insulin secretion from isolated rat pancreatic islets.

8. Combination of ginseng (25, 50 μg/ml) and carbamazepine (10, 20 μmol/l) had no effect on stimulated- insulin secretion On the other hand only combination of ginseng (100 μg/ml) and carbamazepine (40 μmol/l) significantly raised stimulated-insulin secretion. Carbamazepine tended to decrease the action of ginseng on stimulated- insulin secretion.

**In vivo study:**

1. STZ increased serum glucose level and decreased serum insulin level and impaired oral glucose tolerance after oral glucose load.
2. STZ decreased liver glycogen content, increased serum MDA and decreased serum nitric oxide and blood GSH.
3. Gliclazide decreased serum glucose level and increased serum insulin level in STZ – induced diabetic rats. In addition it corrected the impaired glucose tolerance through decreasing serum glucose level and increasing serum insulin level and insulinogenic index.
4. Administration of gliclazide normalized the decrease in liver glycogen content caused by STZ- diabetic rats .Gliclazide also corrected the increase in serum MDA level and the decrease in serum nitric oxide and blood GSH levels in STZ- induced diabetic rats.
5. Carbamazepine had no effects on any of the measured parameters namely serum glucose, insulin, MDA, and nitric oxide and blood GSH, liver glycogen content and glucose tolerance test after 14 days of dose administration in STZ- induce diabetic rats.
6. *Morus alba* decreased serum glucose level and increased serum insulin level in STZ - induced diabetic rats .*Morus alba* failed to

decrease serum glucose level in oral glucose tolerance test although it increased serum insulin level and insulinogenic index.

7. *Morus alba* increased liver glycogen content in STZ –induced diabetic rats .It is to be noted that this effect is less than the effect obtained by gliclazide alone. In addition, *Morus alba* normalized blood MDA, nitric oxide and GSH level in STZ –induced diabetic rats.
8. Ginseng decreased serum glucose level and increased serum insulin level in STZ –induced diabetic rats .This effect is similar to the effect obtained by administration of gliclazide alone. Moreover, ginseng corrected the impaired glucose tolerance through decreasing serum glucose level without affecting serum insulin level
9. Ginseng increased liver glycogen content in STZ- induced diabetic rats .In addition, it decreased the increase in MDA caused by STZ – induced diabetes, normalized serum nitric oxide but had no effect on blood GSH level. It is to be noted that the effect of ginseng on liver glycogen content and oxidative stress biomarkers is less than the effects of administration of gliclazide alone.
10. Combination of carbamazepine and gliclazide decreased serum glucose level and increased serum insulin level in STZ-induced diabetic rats .These effects are similar to the effects of gliclazide alone. This combination slightly ameliorated the impaired glucose tolerance by decreasing serum glucose level without affecting serum insulin level or insulinogenic index.
11. Combination of carbamazepine and gliclazide decreased liver glycogen content in STZ - induced diabetic rats. This effect was less than that of gliclazide alone. It follows that carbamazepine partially antagonized the effect of gliclazide on liver glycogen

content. In addition, this combination corrected the increase serum MDA level and antagonized the decrease in serum nitric oxide and blood GSH level.

12. Combination of carbamazepine and *Morus alba* partially normalized serum glucose and insulin. These actions are similar to the actions of gliclazide or *Morus alba* alone. On the other hand, this combination had no effect on the impaired glucose tolerance.
13. Administration of carbamazepine and *Morus alba* increased liver glycogen content in STZ – induced diabetic rats but this effect was less than the effect of gliclazide alone. Moreover, this combination tended to normalize blood level of oxidative stress biomarkers.
14. Combination of carbamazepine and ginseng tended to normalize serum glucose and insulin levels in STZ – induced diabetic rats. These effects are not better than those obtained by gliclazide alone.
15. Combination of carbamazepine and ginseng tended normalized liver glycogen content as well as serum MDA level .On the other hand, it didn't change both nitric oxide and GSH levels.
16. Combination of gliclazide and *Morus alba* tended to normalize the serum glucose and insulin levels in STZ – induced diabetic rats. *Morus alba* significantly increased the action of gliclazide when they were given concomitantly.
17. Concurrent administration of gliclazide and *Morus alba* tended to normalize liver glycogen content and normalized blood MDA ,nitric oxide and GSH levels .These effects are similar to those obtained by gliclazide alone .
18. Administration of gliclazide and ginseng in STZ- induced diabetic rats tended to normalize both serum and insulin levels and corrected the impaired glucose tolerance but these effects are still not better than those obtained from gliclazide alone.

19. Combination of gliclazide and ginseng normalized liver glycogen content in STZ – induced diabetic rats .Moreover, it normalized blood MDA, nitric oxide and GSH.These effects are similar to the effects obtained by administration of gliclazide alone.
20. Combined administration of *Morus alba* and ginseng reduced serum glucose level and increased serum insulin level in STZ – induced diabetic rats. These effects were better than those obtained by administration of gliclazide alone. There was a significant interaction.
21. Combination of *Morus alba* and ginseng normalized liver glycogen content and the oxidative stress biomarkers in STZ- induced diabetic rats.
22. Combination of gliclazide, carbamazepine and *Morus alba* and combination of gliclazide, carbamazepine and ginseng partially normalized serum glucose and insulin levels .In addition,these combinations tended to normalize liver glycogen content as well as oxidative stress biomarkers.
23. Combination of gliclazide, carbamazepine and *Morus alba* and combination of gliclazide, carbamazepine and ginseng partially ameliorated the impaired glucose tolerance in STZ- induced diabetic rats.
24. Combination of gliclazide, *Morus alba* and ginseng, in half the doses, normalized both serum glucose and insulin levels and corrected the impaired glucose tolerance in STZ- induced diabetic rats.
25. Administration of gliclazide, *Morus alba* and ginseng, in half the doses, to STZ – induced diabetic rats normalized liver glycogen content as well as oxidative stress biomarkers.

26. There was an additive interaction between gliclazide, *Morus alba* and ginseng when administered together in half doses.

## CONCLUSIONS:

**Depending on the results of the present investigation it could be concluded that:**

1. STZ- induced type II diabetes mellitus was associated with oxidative stress
2. *Morus alba*, ginseng or their combination elicited antidiabetic activity almost comparable to gliclazide.
3. The antidiabetic activity of gliclazide, *Morus alba* or ginseng might be related to pancreatic and extrapancreatic effects as well as antioxidant potential.
4. Concurrent use of half the doses of *Morus alba* and ginseng with half the dose of gliclazide synergized its antidiabetic activity and may minimize its possible adverse effects
5. Concurrent use of carbamazepine with gliclazide ,*Morus alba* or ginseng did not significantly alter their antidiabetic effects .

Further clinical investigations are needed to support these findings.

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