EFFECT OF CAMEL’S URINE AND MILK, HONEY WITH NIGELLA SATIVA MIXTURE AND GINGER ON HALOPERIDOL-INDUCED HISTOLOGICAL ALTERATIONS IN DUODENUM OF ALBINO RATS

ABSTRACT:
The present work was performed on 50 male albino rats to study the ameliorative effects of camel’s urine and milk, honey and Nigella sativa mixture and ginger against the toxicity of haloperidol on the duodenal histological of male rats. Rats were divided into five groups (10 rats each). The first group was taken as Control. The second group was intramuscularly injected with 0.1 ml/rat of haloperidol (equivalent to the human therapeutic dose) for 16 weeks, while the other groups; 3, 4, and 5 were treated daily with 0.1 ml of haloperidol and then they were orally given 1 ml of the Camel’s urine and milk, honey and Nigella sativa mixture and ginger, respectively for 16 weeks. The main observed changes after treatment showed haloperidol induced many histopathological alterations on the duodenal tissues, whereas, groups 3-5 revealed significant reduction in the changes induced by haloperidol. Moreover, the Camel’s urine with milk displayed more efficiency in decreasing the toxic effects produced by haloperidol.

INTRODUCTION:
The antipsychotic drugs are classified into several groups. These groups include butyrophenone derivatives, which contain haloperidol. Haloperidol is the most widely used drug in this group (Hollister, 1989; Potter and Hollister, 2001; Tierney et al., 2002). Haloperidol is the first choice for classical antipsychotic medication (Sno and Sohuitenmaker, 2000).

Haloperidol also was used in the treatment of different diseases as rheumatic activity (Grimaldi and Bergonzi, 1980). As regards to the pharmacokinetics of the haloperidol drug, Pakes (1982) found that haloperidol was rapidly absorbed after oral administration (half life 0.4 h) and it was almost completely absorbed even when liquid preparations were used.

The use of drugs with demonstrated efficacy in psychiatric disorders has become widespread since the mid 1950s. Today about 10%-15% of prescriptions written in the United States are for medications intended to affect mental processes to sedate stimulate, or otherwise, change mood, thinking or behavior. This practice reflects both of the high frequency of primary psychiatric disorders and the nearly inevitable emotional reactions of persons with medical illness (Brunton et al., 2005).

Langmead and Rampton (2001) found that the information relating to the possible effectiveness of alternative and complementary medicine is historical. Although there are very few controlled trials proving the beneficial effects of such practice in any disease, over 30% of the Western population now use, some form of complementary and alternative medicine. The single most commonly used modality in most Western surveys is herbal therapy.

Ginger (from the rhizomes of Zingiber officinale roscoe) has been for medicinal purpose for the treatment of a number of diseases (Gruenwald et al., 2000). The pharmacological effects of Zingiber officinale from gingers extracts are reported by Tanabe et al. (1993) and Gong et al. (2004).

Mehaia et al. (1995) studied the chemical composition and nitrogen
distribution of Camel milk from Hamra Camels, in the central region of Saudi Arabia. The average results for pH, and percentage acidity, total solids, fat, protein, lactose and ash for Hamra were 6.63, 0.144, 11.35, 3.22, 2.91, 4.43 and 0.79, respectively. With respect to mineral contents, the levels of Ca, Mg, P, Na and K of Hamra in addition to the Cu, Fe, Mn, and Zn were estimated.

The composition of Camel milk has been studied in various parts of the world including Saudi Arabia (Mehaia and Al-Kanhal, 1989; El-Amin and Wilcox, 1992).

The peculiar feature of Camel is reasonable to investigate some renal functions different from other animals (Maloiy, 1972; Siebert and Macfarlane, 1997) physical examinations were recorded that Camel’s urine contains urea, uric acid, creatinine, chlorides, phosphates, and sulphates (Amer and Alhendi, 1996).

The population of camels in Saudi Arabia is estimated to be 600000 and they are all dromedaries (Chapman, 1991). Camel’s in Saudi Arabia play a major role in supplying the desert dwellers with milk of high nutritional quality and meat under extremely hostile conditions of temperature, drought and lack of pasture (Yagil and Etzion, 1980).

Honey and Nigella sativa were used in medicine (Bergman et al., 1983; Elkhadi and Khandil, 1986; Ali et al., 1997). These authors revealed that the honey and Nigella sativa have anti-inflammatory, anticancer antithrombotic and cardiovascular effects.

**MATERIAL AND METHODS:**

The drug:

The anti-dopaminergic agent haloperidol was purchased from janssen Pharmaceutica, registration 016395, J.PH. 2000.

Honey and Nigella sativa:

95 g of Alfagra honey from Almadina Almonawara was mixed with 5g of Nigela sativa powder in 100 ml BW from wadi alnah market was used according to EL-Dakhakhiny (1982) method.

Ginger solution:

The fresh ginger rhizomes (Zingibar officinale Rose) were obtained from a local market and were prepared as described by Shati and Elsaid (2009) method.

Camel’s milk and urine:

Milk and urine were taken from female Humra camels at the morning from Jeddah south conservation of Saudi Arabia and used according to Khalifa (2006) method.

**Animals:**

Fifty adult male albino rats (Rattus norvegicus) each being of approximately 250 g body weight and 56 days old were used in the present experiments. They were maintained on a standard diet and kept under suitable conditions during the whole period of experimentation, and were allocated into seven groups as follow:

**Group 1:**

It served as control group. Rats were intramuscularly injected with 0.1 ml of drug solvent (corn oil) every 4 weeks for 16 weeks.

**Group 2:**

Rats were intramuscularly injected with a dose equivalent to the cumulative human therapeutic dose (0.1 ml) of haloperidol drug every 4 weeks for 16 weeks according to Brunton et al. (2005) and calculated to rats according to Paget and Barnes (1964).

**Group 3:**

Rats were intramuscularly injected with 0.1 ml of haloperidol and orally administered 1.0 ml of a mixture of camel’s urine and milk.

**Group 4:**

Rats were intramuscularly injected with 0.1 ml of haloperidol and orally administered 1.0 ml of ginger extract.

**Group 5:**

Rats were intramuscularly injected with 0.1 ml of haloperidol and orally administered 1.0 ml of a mixture of honey with Nigella sativa.

Rats of the experimental and control groups rats were sacrificed experimentation period. The duodenum was rapidly excised and cut into small pieces and immediately fixed in 10% buffered formalin for haematoxylin and eosin staining and examined using light microscope.

**RESULTS:**

Microscopically examination of the duodenum of control group showed no histopathological changes (Figs 1 & 2).
Figs 1&2. Photomicrograph of a transverse section of control duodenum of male albino rats shows normal histological structure of the duodenum. ×100 & ×400, respectively.

In the haloperidol-treated group, 16 weeks after treatment, the duodenum revealed vacuolar degeneration in macrovilli layer and proliferation of submucosa layer (Figs 3 & 4). Decreased mucous glands in mucosa layer and degeneration with necrotic cells were observed (Fig. 5).

Figs 3&4. Photomicrograph of a transverse section of haloperidol duodenum rats shows vacular degeneration in mucosal cells and proliferation of submucosa layer. ×100 & ×400, respectively.

Fig. 5. Photomicrograph of a transverse section of haloperidol duodenum rats show decreased mucous glands in mucous layer and necrotic cells. × 400.

Some of the macrovilli appeared with deformed shape and lost their apical portion with necrotic cells (Figs 6&7) lymphocytic infiltration in submucosa layer and increase in the number of goblet cells were observed (Fig. 8). Both mucosal and submucosal layers were destroyed and most of the cells were necrotic and others appeared with cytoplasmic vaculation (Figs 9&10).

Figs 6&7. Photomicrograph of a transverse section of haloperidol duodenum rats shows deformed mucosal cells with necrotic cells. ×100 & ×400, respectively.

Fig. 6. Photomicrograph of a transverse section of haloperidol duodenum rats shows deformed mucosal cells. ×100.

Fig. 7. Photomicrograph of a transverse section of haloperidol duodenum rats shows deformed mucosal cells. ×400.
Fig. 8. Photomicrograph of a transverse section of haloperidol duodenum rats shows lymphocytes and goblet cells. ×400.

Fig. 9 & 10. Photomicrograph of a transverse section of haloperidol duodenum rats shows lymphocytes in sub mucosa layer and in the mucosal cells. ×100 & ×400, respectively.

In the mixture of camel’s urine with milk and drug treated duodenum rats (Figs 11 & 12) the examination revealed normal intestine tissue.

Figs 11 & 12. Photomicrograph of a transverse section of haloperidol duodenum rats received camel’s urine with milk shows normal duodenum tissue. ×100 & ×400, respectively.

Honey with Nigella sativa mixture and drug treated duodenum rats (Figs 13 & 14) the examination revealed mild improvement in the intestine tissue, where some mucosal cells still showed histopathological alterations.

Figs 13 & 14. Photomicrograph of a transverse section of haloperidol duodenum rats received camel’s urine with milk shows normal duodenum tissue. ×100 & ×400, respectively.

In the mixture of camel’s urine with milk and drug treated duodenum rats (Figs 11 & 12) the examination revealed normal intestine tissue.
DISCUSSION:

The present study was designed to investigate the adverse effects of haloperidol drug on duodenum of rats. The present results showed that treatment with haloperidol for 16 weeks induced adverse effects in duodenum, vacuolar degeneration in macrovili and proliferation of submucosa layer, decreased mucus glands, necroses and lymphocytic infiltrations.

These findings are strongly supported by Mitchell et al. (2002) who reported that acute administration with a large dose of haloperidol resulted in a microglial response indicative of neuronal damage. In another study, DNA isolated from haloperidol treated cell was degenerated an indication of a necrotic rather than an apoptotic pathway of cell death (Behl et al., 1995).

It was well documented that chronic treatment with haloperidol guinea pigs causes smaller and heterochromatic nuclei of neurons, denser cytoplasm, lysosomes and lipofuscin pigment granules, perinuclear edema and large vacuolar structures in the perikaryon. Increased haloperidol doses were reported to cause pyknotic nuclei, myelin degeneration and decreased number of viable neurons (Ozbek et al., 2000).

Conversely, the present experiment demonstrated that alteration in the duodenum histological structure of rats who received the drug with one of the following therapies camel’s milk and urine mixture, ginger, honey with Nigella sativa exhibited marked reduction; furthermore, the duodenum of rats took mixture of camel’s milk and urine with the drug revealed more improvement than other therapies.

These results agree with those obtained by Weiner (1986) and Obaseiki and Afonya (1984) who reported that the therapeutic potential of honey with Nigella sativa mixture possesses detoxifying, antioxidant, antiinflammatory characters.

Oryan and Zaker (1998) showed that the application of honey on cutaneous wound of rabbits resulted in reduction in the number of the inflammatory cells, oedematous fluid, and tissue necrosis.

With regard to chemical composition of the Arabian camel urine, Muhammad (1998) stated that camel’s urine have high levels of potassium and proteins; it has effectiveness as fibrinolytic factor, and as a drug of useful antimicrobial activity and efficiency. Recently, further studies on the chemical constitution of camel urine declared that camel urine contains high concentrations of potassium, urea and proteins, as well as low concentration of uric acid, creatine and sodium (Ba’Smaeel, 2004).


High minerals content (sodium, potassium, iron, zinc, copper, and magnesium) as well as a high vitamin C intake may act as antioxidant, thereby removing free radicals,
which may provide a stress situation to the animals (Gast et al., 1969; Knoess, 1979).

Along a similar line, Zerumbone (ZER), a sesquiterpene from the edible plant Zingibar Zerumbet, is recognized as a chemical agent that disrupts the assembly and / or activity of NAD pH oxidase in DMSO differentiated HL-60 cells (Heitzer et al., 1999). A kira et al. (2002) indicated that (ZER) is a phytochemical that has distinct potentials for use in anti-inflammatory, chemoprevention, food and chemotherapy.

Similar study was done by Khalifa (2006) who demonstrated that the toxic effects of haloperidol drug on testicular tissue was improved in animals took mixture of camel's urine with milk and ginger then the rats were given camel's urine, milk and honey with *Nigella sativa* mixture, respectively. Similar study was also done by AL-Elyani (2007) found that the mixture of honey with *Nigella sativa* displayed more efficiency in decreasing the toxic effects produced by haloperidol in kidney tissue.

In conclusion, the results revealed the toxic effect of haloperidol on duodenum tissue. The mixture of camel's milk and urine is more efficiency in decreasing the toxic effects produced by the drug.

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Mehaia MA, Hablas MA, Abdel-Rahman KA, El-Mougy SA. 1995. Milk composition of...
تأثير كل من أورال الإبل وأليها وخلط العسل مع الجبة السوداء والبرجيل في التخفيف من سمية عقار مضاد الأكثناك (الهالوبيردول) على الأثي عسر لذكور الفئران البضاء

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المجموعة الأولى: وتم عمل التجربة على عدد من الفئران البضاء والمجموعة الثانية: وتم عمل التجربة على عدد من الفئران البضاء.

ال مجموعة الثالثة: وتم عمل التجربة على عدد من الفئران البضاء.

ال مجموعة الرابعة: وتم عمل التجربة على عدد من الفئران البضاء.

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التعليمات: لا يوجد نص يمكن قراءته بشكل طبيعي من الصورة المقدمة.