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Acute effects of *Fraxinus excelsior* L. seed extract on postprandial glycemia and insulin secretion on healthy volunteers

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ABSTRACT

Aim of the study: Fraxinus excelsior L. (Family: Oleaceae) seeds are consumed as a food, condiment, and folk medicine. The seeds are traditionally used as a potent hypoglycemic agent, but no clinical evidence exists in as to this regard. We assessed the clinical efficacy and safety of the seed extract (FraxiPure™, Naturex), containing 6.8% of nuzhenide and 5.8% of GI3 (w/w), on plasma glucose and insulin levels against glucose (50 g) induced postprandial glycemia.

Materials and methods: Preselected dose (1.0 g) was used in a double blind, randomized, crossover, placebo (wheat bran) controlled study on 16 healthy volunteers. Each treatment was given immediately after a fasting blood glucose sample (0 min). Postprandial plasma glucose levels were estimated at 0, 15, 30, 45, 60, 90 and 120 min; and postprandial plasma insulin at 0, 30, 60, 90 and 120 min.

Results: The extract lowered the incremental postprandial plasma glucose concentration as compared to placebo at 45 min ($P = 0.06$) and 120 min ($P = 0.07$). It statistically ($P = 0.02$) reduced the glycemic area under the blood glucose curve. The seed, also, induced a significant ($P = 0.002$) secretion of insulin at 90 min after glucose administration. However, the insulinemic area under the blood insulin curve was not different than the placebo. No adverse events were reported.

Conclusions: Our findings confirm the hypoglycemic action of *Fraxinus excelsior* L. seed extract. These promising results, thus, encourage conducting long-term clinical studies to further evaluate the efficacy and safety of *Fraxinus excelsior* L. seed extract in healthy and diabetic volunteers and also to explore the possible mechanism(s) of action.

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1. Introduction

Plant derivatives with purported hypoglycemic properties have been used in folk medicine and traditional healing systems around the world (e.g., Native American, Indian, Jewish, Chinese, East Indian, Mexican) (Ungar, 1957; Yeh et al., 2003). But on the other hand, as indicated by Marles and Farnsworth (1995), not all of the plants, based on anecdotal use, reported to be entirely safe, and they emphasize the need for carefully planned scientific research to identify those hypoglycemic plants with true therapeutic efficacy and safety. To provide evidence-based herbal medicine, we must standardize suitable clinical models and utilize randomized controlled trials (RCTs) to determine what herbs are efficacious for what diseases and standardized them according to their health use.

In this pursuit, the present study, utilizing our well-standardized acute clinical model, was undertaken with the common ash, *Fraxinus excelsior* L. (Family: Oleaceae). It grows naturally in Europe, North Africa, and Asia from the shores of the Atlantic Ocean in the West to the Volga River in the East (Pliûra and Heuertz, 2003; Eddouks et al., 2005). Several reports reveal that the seeds of *Fraxinus excelsior* L. have been traditionally used as food, condiment, and folk medicine (Hedrick, 1919; Kunkel, 1984; Boisvert, 2003). The ash tree is known in Morocco as "Lissan Ettir", and its seeds as "L'ssane l'ousfour", one of the ingredients of the condiment "Ras el Hanout" used to prepare the famous tagines and other typical Moroccan plates (Sinclair, 1998; Vergne, 2001; Allen, 2007). In The Netherlands, there is evidence of the use of ash seeds since the medieval 16th century (Vermeeren and Gumbert, 2008). In Iran, the ash seeds are employed as carminative and to destroy

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bladder stones (Parsa, 1959). Also, in Morocco the aqueous extract of the ash seeds is drunk in order to enhance several health conditions (Eddouks and Maghrani, 2004). This plant has been reported to have anti-oxidative (Meyer et al., 1995; Schempp et al., 2000; Middleton et al., 2005), anti-inflammatory (El-Ghazaly et al., 1992; von Kruedener et al., 1996), anti-rheumatic (von Kruedener et al., 1995; Gundermann and Müller, 2007), analgesic (Okpanyi et al., 1989), and antipyretic (Strehl et al., 1995) properties. The seeds of *Fraxinus excelsior* L. were recognized as potent hypoglycemic agents by several traditional healers using it for type 1 and type 2 diabetes mellitus (Eddouks et al., 2005). Eddouks and Maghrani (2004) and Maghrani et al. (2004) experimented on animals and reported hypoglycemic activity in normal rats and anti-diabetic properties, such as controlling streptozotocin (STZ) induced hyperglycemia, but no clinical evidence and scientific validation exist in this regard.

Therefore, in the current acute clinical study, for the first time an attempt has been made to confirm our hypothesis that *Fraxinus excelsior* L. seed extract will reduce postprandial glycemia in non-diabetic healthy individuals following glucose (50 g) intake. In order to determine the underlying mechanism, the serum insulin concentrations were also determined. We are thus; presenting the preliminary data on the acute clinical effect of the aqueous extract of the seeds of *Fraxinus excelsior* L. on healthy subjects against glucose induced postprandial glycemia.

2. Materials and methods

2.1. Fraxinus excelsior L. seed extract

2.1.1. Raw material

The seeds of *Fraxinus excelsior* L. were collected from many rural communities in Morocco and deposited at the herbarium (voucher specimen # J02/02/A7; reference # RB3524) of Naturex Maroc, Technopole Nouasser BP 42, Casablanca 20240, Morocco. First the samaras were harvested from the trees in the Atlas Mountains, and then the seeds were separated manually at home, a traditional practice in that region. After the collection, the seeds were analyzed in order to confirm their botanical origin. Analyses included macroscopic, microscopic and high pressure thin layer chromatography (HPTLC, CAMAG, Switzerland) techniques. These analyses were conducted by Mr. Elan Sudberg from Alkemists Pharmaceuticals, Inc. (Costa Mesa, CA, USA) using authenticated *Fraxinus excelsior* L. seeds as a control. The sample used in our experiment corresponded to the seeds of *Fraxinus excelsior* L.

2.1.2. Extract preparation

Fraxinus excelsior L. seed extract was obtained by an industrial process (FraxiPure™, batch # 347/53/A7; reference # 149251, Naturex SA, Site d'Agroparc BP 1218, 84911 Avignon Cedex 9, France) according to the traditional method used in Morocco (Eddouks and Maghrani, 2004; Maghrani et al., 2004; Eddouks et al., 2005). First the seeds were milled, and then the seed powder was extracted in water stirring for 2 h at 65 °C. The ratio (*Fraxinus excelsior* L. seeds: solvent) was fixed, using only water as a solvent. After filtration, the clarified solution was concentrated under vacuum at 40 °C which was then mixed with Arabic gum and silicon dioxide as carriers and spray dried to obtain a fine powder. Moisture content in the extract was less than 8%. The extract ratio was approximately 6:1 (*Fraxinus excelsior* L. seeds: extract powder), yielding 16.67% of dry *Fraxinus excelsior* L. seed extract.

2.1.3. Chemical identification

The molecular weight of nuzhenide (β-D-glucopyranoside, 2-(4-hydroxyphenyl)ethyl, 6-[(2S,3E,4S)-3-ethylidene-2-(β-D-glucopyranosyloxy)-3,4-dihydro-5-(methoxycarbonyl)-2H-pyran-4-acetate]) and GI3 (2H-pyran-4-acetic acid, 3-ethylidene-2-(β-D-glucopyranosyloxy)-3,4-dihydro-5-(methoxycarbonyl)-, 4-[2-[[6-O-[[3-ethylidene-2-(β-D-glucopyranosyloxy)-3,4-dihydro-5-(methoxycarbonyl)-2H-pyran-4-yl]acetyl]-β-D-glucopyranosyl]oxy]ethyl]phenyl ester, stereoisomer (9CI)), the main secoiridoids being standardized in *Fraxinus excelsior* L. seed extract, were identified by HPLC–MS and the chemical structures were determined by comparison of NMR data to those in literature (LaLonde et al., 1976). Fig. 1 shows the chromatogram of the extract and the chemical structure of the two compounds. An HPLC method was developed for the quantification of the secoiridoid contents. The HPLC system used was an Agilent 1100 (Palo Alto, CA, USA) equipped with a diode array detector. The stationary phase was a Prodigy ODS3 analytical column (250 × 4.6 mm i.d., 5 μm, Phenomenex, Torrance, CA, USA) thermostated at 30 °C. The flow rate was 1 ml/min, and the elution was monitored at 238 nm. The mobile phases were (A) water with 0.1% TFA and (B) acetonitrile. The solution of 80% A and 20% B was maintained for 5 min and then changed to 70% A and 30% B after 15 min total time; followed by a linear gradient of 100% B after 25 min total time, maintaining this composition for 10 min; the system was then reequilibrated to the initial composition after 10 min. Peaks of nuzhenide and GI3 appeared at approximately 13 and 18 min, respectively. The *Fraxinus excelsior* L. seed extract used in this clinical trial contained 6.8% of nuzhenide and 5.8% of GI3.

2.2. Clinical trial

2.2.1. Test material

The dose of *Fraxinus excelsior* L. seed extract in our acute clinical study was 1.0 g (powdered extract filled in two capsules of 500 mg each).

2.2.2. Placebo

Wheat bran (Certified Hard Red Wheat Bran; lot 195) served as placebo which was also administered at the dose of 1.0 g for comparison. It is certified by American Association of Cereal Chemists (AACC). The main composition of wheat bran consists of protein – 16.05% (Nx6.31), fat – 4.34% (as triglycerides, total), total dietary fiber – 49.65%, carbohydrates – 65.75%, starch – 13.3% (Modified Ewers method), besides vitamin B_1, B_6, B_{12}, magnesium, potassium, phosphorus, manganese, calcium, copper, iron, sodium and zinc. It did not seem to improve blood glucose control or risk factors for coronary heart disease (CHD) in type 2 diabetes over 3 months (Jenkins et al., 2002).

2.3. Study design

The study was randomized, double blind, placebo-controlled and crossover designed. By this design subjects act as their own controls. Only the "blinder", an independent clinical research scientist, knew the identity of the treatments who performed and maintained the "blinding" of packages, labels, and randomization of the treatments while not having contact with individuals or data. Randomization was done using a random number table. Monitoring of all individual records, data sheets, sample handling, laboratory sample storage, and sample inventory for completeness and adherence to the protocol was conducted by the study monitor.

The trial was carried out at Kumar Clinic and Diabetes Care Centre, Lucknow, India. All the healthy subjects were recruited at this Centre.

2.3.1. Inclusion criteria

- Subjects were males or non-pregnant females aged 18–55 years, recruited from India.

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