University of Sulaimani
College of Pharmacy
Department of Pharmacology and Toxicology

Proposal for research project submitted to the Department of Pharmacology and Toxicology-College of Pharmacy.

A Pilot clinical study of the effect of resveratrol on serum level of type II Collagen (Coll 2-1) and Aggrecan biomarkers in patient with knee Osteoarthritis.

Background:

The treatment of knee osteoarthritis (OA) still remains a challenge. There is a need not only for efficacious and safe treatments but also for specific and reliable biomarkers that would help observing both the progression of the disease and treatment efficacy.

Resveratrol; extracted from Polygonum cuspidatum, is a natural phytoalexin that is found in the grape skin, berries and peanuts. It is considered as a rational herbal candidate with a potential therapeutic interest in joint disorder, it also shows pleiotropic effects. Its anti-inflammatory and OA-protective effects has documented in many studies. Pre-clinical studies provided accumulating evidence on resveratrol efficacy in ameliorating the degenerative articular damage. Recently a clinical study demonstrated the efficacy of resveratrol as an add-on therapy in alleviating pain and reduction of inflammatory biomarkers. However, no clinical trials are existing to date to determine the effectiveness of resveratrol as a monotherapy in articular disorders particularly in knee OA and investigating specific biomarkers of cartilage degradation. For this purpose, this study has designed to assess the clinical efficacy of oral resveratrol and observing serum level of both type II Collagen (Coll 2-1) "a biomarker of collagen network degradation" and aggrecan "a degradation product of articular cartilage" biomarkers in patients with mild and moderate knee osteoarthritis.

Aim: The aim of this pilot open labeled-non-controlled clinical trial is to investigate the effects of oral administration of resveratrol (formulated as an oral capsule dosage form) in patients with mild or moderate knee OA on the serum levels of specific biomarkers of OA "Coll 2-1 and aggrecan"and on the evaluation of pain.

Methodology

Patients and Setting

The study will be conducted at the Shar teaching hospital of Sulaimani city in accordance with the Declaration of Helsinki and its amendments, and the Guidelines for Good Clinical Practices issued by the Committee of Propriety Medicinal Products of the European Union. The study will be non-randomized open-labelled non-controlled clinical trial, it will be carried out in accordance with the Ethical Guidelines for Human Studies and the currently adopted regulations of the Iraqi MOH. Permission will be obtained from the ethical committee of College of Medicine-University of Sulaimani. All patients should give a written informed consent to participate. The study will be a 12-week of administration of oral Resveratrol (500mg/day in single dose) alone in patients with mild to moderate osteoarthritis. A rescue medication (500mg of acetaminophen and up to four tablets per day) will be allowed to the patients for non-tolerated pain they will experience during the study period.

Inclusion Criteria:

- Eligible patients (expected sample 35-40 patients) will be selected among those who has mild to moderate OA at both screening and baseline visits, as defined by the up-to-date revised American College of Rheumatology (ACR) criteria for diagnosis of knee OA.

Exclusion criteria:

- Patients with a history of rheumatoid arthritis, gout, severe ischaemic heart disease, heart failure, hepatic failure, renal failure.
- Consumption of non-steroidal anti-inflammatory drugs or corticosteroid drugs within 4 weeks of study, intra-articular injection within 3 months prior to the study recruitment.
- Pregnant or desire to become or lactating women.

Patients will be selected to receive Resveratrol 500mg/day in capsule dosage form (specially prepared for this purpose, in single dose) alone.

Primary outcome measure:

The serum levels of Coll-2-1 and aggrecan will be determined before treatment (at day 0) and after 90 days of treatment using Enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer instructions. Additionally, biomarkers of inflammation (using Enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer instructions) will also be evaluated twice at baseline at Day 0 (pre-treatment) and at day 90 (post treatment).

Standard haematological profile (utilizing the Swelab Alfa Plus system) and both liver and kidney functions markers (liver and kidney function tests), and lipid profiles will be carried out

spectrophotometrically at baseline and at the end of the treatment using the clinical chemistry analyzer Cobas c 311, utilizing ready-made kits according to the manufacturer's recommendations for evaluating safety and tolerability of resveratrol.

Secondary outcome measure:

Disease activity will be clinically assessed at the baseline (day 0) and at 30-days intervals that will be at monthly basis "1st month, 2nd month and 3rd month of this study. Efficacy is assessed using the adopted scoring systems of visual analogue scale for pain (VAS) and Knee injury and Osteoarthritis Outcome Score (KOOS). Assessment criteria is based on changes from baseline observed to the end of month three.

Requirements:

1. Hospital Facilities for diagnosis and treatment of patients with Knee OA and follow up utilizing KOOS scoring system.
2. Resveratrol (standardized crude powder 98% pure according to HPLC) formulated in suitable oral dosage form (capsules).
3. Laboratory equipment for measurement of serum level of Coll-2-1 and aggrecan as well as the other inflammatory biomarkers.

Statistical analysis:

Statistical analysis of results will be basically performed by using GraphPad prism softwares. Comparison of pre- and post-treatment results of the study groups will be carried out using a t-test.

Time required:

A total of 6 months; including preliminary work, analysis of data and writing the manuscript is needed.

Estimated cost of the project:

The cost of project will be approximately 5000 US $ it will be covered by the researcher.

Reference:

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Participation:

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