Methods: We performed a descriptive cross sectional study. We included patients with confirmed diagnosis of OA alone or in coexistence with rheumatoid arthritis (RA). Patients were followed during a 12 month period for AE. Adverse events were classified according CTCAE to the Common Terminology Criteria for Adverse Events. Descriptive epidemiology for continuous variables, measure of central tendency and dispersion for qualitative and categorical variables through percentages and averages were calculated; we analyzed some bi-variated correlations with X2 test.
Results: We included 360 patients 61% (220) with diagnosis of osteoarthritis alone and 39% (140) with OA in coexistence with rheumatoid arthritis. The mean age was 69.4 ± 6.7 years; most of patients were between 60 and 80 years old, 86% were women. From the total of patients 91% were polymedicated (received more than three drugs) and were taking 100 mg of Diacerein daily. During the 12 month follow-up period there were 37 adverse events (in 10.2% of patients), 25 in the group with OA alone and 12 in the group with OA in coexistence with RA. The most common adverse event was dyspepsia (13/37 - 3.6% of patients), followed by diarrhea (10/37 - 2.8% of patients), nausea (5/37 - 1.4% of patients), epigastric pain (3/37 - 0.8% of patients), abdominal pain (2/37 - 0.5% of patients), elevated alanine aminotransferase (2/37 - 0.5% of patients), dysuria (1/37 - 0.3% of patients) and tachycardia (1/37 - 0.3% of patients). According to the CTCAE to the Common Terminology Criteria for Adverse Events classification most of these adverse events were mild 95% and 5% severe; and predominantly gastrointestinal AE. There were no statistical correlation between age groups or polymedicated groups and adverse events; there were no statistical differences between OA alone and OA plus RA treatment groups; surprisingly nobody reported changes in urine coloration, an AE that is very common in other reports.
Conclusions: Gastrointestinal adverse events were observed mainly, but in a small portion of the patients. Diarrhea was not present as previously described in the literature. On the other hand, it is noteworthy that even in those patients who were taking medications concomitantly for rheumatoid arthritis there was no increase in the frequency of adverse events. For this reason Diacerein can be considered a safe medication for the treatment of OA. Obviously, it is necessary to carry out more long-term follow-up studies to evaluate the safety and effectiveness of the Diacerein.

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CHONDROPROTECTIVE EFFECT OF GINGER/TURMERIC TREATMENT IN MIA INDUCED OSTEOARTHRITIS RAT MODEL

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Purpose: Osteoarthritis (OA) is a complex disease of the whole joint. Herbal treatment may have a chondroprotective and therapeutic effects in OA. We investigated the mechanism of action of a new herbal formula prepared from equal proportions of ginger (*Zingiber officinale Rosc.)* and turmeric (*Curcuma longa L.*) rhizomes cultivated in Egypt.
Methods: Thirty-five albino rats were intra-articularly injected with Monosodium Iodoacetate in the knee joint. Ginger and turmeric at 1:1 ratio was orally administered at doses of 200 and 400 mg/kg (F200 and F400). Serum levels of cartilage oligomeric matrix protein (COMP), hyaluronic acid (HA), malondialdehyde (MDA), myeloperoxidase (MPO), Interleukin-1 beta (IL-1β) and superoxide dismutase activity (SOD) were measured using ELISA. The composition of the herbal formula hydro-ethanolic extract was characterized using UPLC-ESI-MS.. Histopathological changes in affected joints were examined using H & E staining. Statistical analysis was performed using one-way ANOVA.
Results: Fragmentation behaviors of the compounds identified eleven curcumin and gingerol derivatives. Serum level of COMP, HA, MPO, MDA, and IL-1β was significantly decreased in F 200, F 400 and V groups when compared to OA group (P value < 0.0001). On the other hand SOD levels were significantly elevated in treated groups compared to OA groups (P value < 0.0001).
Conclusions: Composition and characterization of herbal formula hydro-ethanolic extract confirmed identification of eleven curcumin and gingerol derivatives. The ginger/turmeric at 1:1 had chondroprotective effect via anti-inflammatory and antioxidant effect in rat OA model. Further pharmacological and clinical studies are needed to evaluate this effect.

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EFFICACY AND BIODISTRIBUTION OF AUTOLOGOUS, ALLOGENEIC, AND XENOGENEIC ADIPOSE MESENCHYMAL STEM CELLS ON OSTEOARTHRITIS

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Purpose: To investigate efficacy and to correlate it with in vivo biodistribution of autologous, allogeneic, and xenogeneic adipose MSCs on osteoarthritis.
Methods: MSCs were isolated from different species of adipose tissue. All animals received humane care in compliance with the "Guide for Care of Laboratory Animals" formulated by the National Ministry of Science (2006). Autologous cells and SVF were isolated from sheep while allogeneic cells were derived from sheep and SD rats, respectively. Xenogeneic cells were come from human AD-MSC. PRP was prepared by harvesting autologous blood from each animal before the induction of anaesthesia. OA were induced in large animals of sheep and New Zealand white rabbits, by anterior cruciate ligament transaction (ACLT) and medial meniscectomy of right knee while in SD rats OA were induced by medial meniscectomy. For efficacy study, all animals were sacrificed at 12 weeks post injection. For biodistribution study, MSCs were labeled with superparamagnetic iron oxides (SPIO) or fluorescence dye. Magnetic resonance imaging (MRI), real-time PCR, macroscopic examination, histological analysis, fluorescence in situ hybridization (FISH) were used to investigate the cell fate and efficacy.
Results: Macroscopic evaluations showed that autologous (5×10^7), allogeneic (5×10^7), and xenogeneic (2.5×10^6) MSC treatment in sheep and rabbit models, respectively, ICRS scores demonstrated that efficacy of autologous adipose MSCs is better than autologous SVF and HA while allogeneic MSCs exhibit better efficacy than PRP and HA. When treated with xenogeneic MSCs, ICRS scores was increased compared with HA treatment. Detection thresholds of the labelled MSCs in vitro and in vivo were determined to be 10^2-10^4 and 10^3-10^5 cells, respectively. MRI results demonstrated that signals of autologous AD-MSCs labeled with SPIO lasted 18 weeks in sheep knee joint while signals of labeled allogeneic AD-MSC lasted 14 weeks in sheep knee joint under T2* sequence. Xenogeneic AD-MSCs labeled with a florescent dye (DiD) remained relatively stable in OA joints and became undetectable after 70 days of injection while in the healthy joints the signal diminished rather quickly at day 28. In order to detect organ distribution, 2.5×10^6 male allogeneic rat adipose MSCs, 2.5×10^6 human adipose MSCs were injected into female SD rat OA knee joint. At the 49 days post injection, male donor DNAs were still present in the injected knee joints, but not in any other tissues/organs. In the xenotransplantation 14 days post injection, human DNAs were found in muscle and ligament of OA joints while at 70 days after injection, human DNAs were only found in meniscus. Allogeneic and xenogeneic cell DNA were not found in distant organs including heart, liver, spleen, lung, kidney, brain, and ovary. To gain further understanding of the biodistribution of MSCs in the injected joints at the histology and cellular level, we labeled autologous sheep MSCs and injected into joints of the same sheep, SIPO signals were found at meniscus. When labeled allogeneic raMSCs were injected, SPIO signals were found at subchondral bone and meniscus. At 3 days post injection confocal microscopy showed that SPIO+ cells were in the lining of synovial membrane, and were not all co-labeled with CD68, indicating that SPIO signals were not all taken by macrophages (CD68+) via phagocytosis. FISH using Y chromosome probe exhibited allogeneic male raMSCs were found at synovium and subchondral bone. When human MSCs were injected, human mitochondria signals were detected in both meniscus and cartilage with haMSC treatment. Human cells undergoing proliferation by ki67 activity were detected in the joint tissues of haMSC treatment groups. Proteomics of allogeneic MSC treatment detected more than 1,800 proteins in cartilage showing part of the proteins were up-regulated while part of the proteins were down-regulated compared with untreated group.
Conclusions: The current study demonstrated PK profile of labeled autologous, allogeneic, and xenogeneic adipose MSCs after IA injection in immunocompetent, surgery-induced OA animal models. Moreover, signals of labeled autologous, allogeneic, and xenogeneic AD-MSC in OA animal models lasted for about 10 weeks, 14 weeks, and 18 weeks in the knee joint at the same time efficacy was observed, respectively.