<table>
<thead>
<tr>
<th>Study</th>
<th>OA model</th>
<th>Group description</th>
<th>Tests used</th>
<th>Results</th>
</tr>
</thead>
</table>
| Rodrigues et al, 2017 (22) | Sodium MIA: 2 mg in the knee of Wistar rats | Five groups with 6 animals each:  
- SrRan 25 mg·kg⁻¹·d⁻¹ prophylactically PO (28 days before induction);  
- SrRan 25 mg·kg⁻¹·d⁻¹ for treatment (28 days after induction);  
- SrRan 50 mg·kg⁻¹·d⁻¹ for treatment (28 days after induction);  
- 0.9 % saline;  
- Control: no intervention | Joint incapacitation (Weight bearing test); mechanical hyperalgesia (Randall Selitto test) and motor activity (Rotarod test) on days 0, 7, 14, 21, and 28. | SrRan did not promote analgesia in the prophylactic and treated groups at the doses tested. |
| Alves et al, 2017 (32) | Zymosan: 2 mg in TMJ of Wistar rats 1 h after treatment with SrRan | Seven groups with 6 animals each:  
- Sham: no induction and receiving 0.9 % saline PO;  
- Control: indomethacin 5 mg·kg⁻¹;  
- Pretreated with zinc protoporphyrin IX 3 mg/kg, followed by SrRan 0.5 mg·kg⁻¹·d⁻¹ after 30 min PO  
- 3 groups: SrRan 0.5, 5, and 50 mg·kg⁻¹·d⁻¹ each  
- 1 group without treatment  
Period: 3 months | Von Frey test at the 4th hour after induction; Myeloperoxidase activity; Evans Blue Extravasation Assay; histopathological analysis; cytolocal evaluation for polymorphonuclear joint wash; immunohistochemical analysis and ELISA for TNF-α and IL-1β | Reduction of mechanical hypernociception with the use of SrRan, possibly by reduction of TNF-α expression in the periarticular tissue and trigeminal ganglia, without impact on the other inflammatory parameters evaluated. |
| Mierzwa et al, 2017 (33) | OVX in Wistar rats at 6 months of age. | Five groups with 10 animals each:  
- Control: O VX + saline;  
- SrRan300: O VX + SrRan 300 mg·kg⁻¹·d⁻¹ PO;  
- SrRan625: O VX + SrRan 625 mg·kg⁻¹·d⁻¹ PO;  
- MV: O VX + M V;  
- SrRan625 + MV: SrRan 625 mg·kg⁻¹·d⁻¹ with MV  
Period: 3 months | Histological analysis of femoral articular cartilage using the OARSI score; quantitative evaluation of glycosaminoglycan sulfate and hyaluronic acid; immunohistochemical analysis for caspase 3, collagen type II, TNF-α, and MMP-9 | Increased expression of caspase-3 in MV group with SrRan 625 mg·kg⁻¹·d⁻¹. SrRan alone at a dose of 300 mg·kg⁻¹·d⁻¹ reduced caspase-3 expression and OARSI score. No reduction of TNF-α expression. |
| Nunes et al, 2015 (34) | ACLT in Wistar rats and group with injection of zymosan 1 mg in knee. | Nine groups with 6 rats each:  
- Zymosan-induced group: 30 mg/kg 30 min before induction;  
- Zymosan-induced group: 300 mg/kg 30 min before induction;  
- Control: intra-articular saline and PO;  
- Naïve: only received saline PO;  
- A C L T + SrRan (A1): 300 mg/kg of SrRan between the 1st and 4th days;  
- A C L T + Saline (A2): saline between the 1st and 4th days;  
- A C L T + SrRan (B1) 300 mg/kg/day on the 14th and 16th days;  
- A C L T + Saline (B2): saline on the 14th and 16th days;  
- Sham: no transection + Saline. In addition, groups received naloxone 2 mg/kg SC 30 minutes prior to administration of SrRan. | PET in the forced ambulation test and Von Frey test at the 4th hour after induction with zymosan; PET at the 4th hour after administration on day 4 in groups A1 and A2; Von Frey test in the 0, 2nd, 4th, and 6th hours of days 14 and 16 and only once a day on the other days in groups B1 and B2; Cytology analysis and ELISA for TNF-α, IL-1β and CINC-1 of synovial fluid. | Reduction of PET with SrRan in zymosan-induced groups. Dose of 300 mg·kg⁻¹·d⁻¹ decreased joint pain by the Von Frey test, with no change in influx of inflammatory cells to the joint compared to saline. SrRan increased paw withdrawal threshold in operated groups. Reversal of effects of SrRan with naloxone. Decreased TNF-α and IL-1β expression after zymosan-induced OA with SrRan. |
| Pelletier et al, 2012 (35) | A C L T in female dogs aged 1-3 years. | Four groups with 10 animals each:  
- Group 1: placebo;  
- Group 2: SrRan 25 mg·kg⁻¹·d⁻¹;  
- Group 3: SrRan 50 mg·kg⁻¹·d⁻¹;  
- Group 4: SrRan 75 mg·kg⁻¹·d⁻¹. The treatment was performed between the 4th and 12th week after induction. | Plasma and synovial fluid levels of SrRan. Macroscopic and microscopic classification (OARSI) of the lesions. Histomorphometric analysis of subchondral bone. PCR for quantification of MMP-1, MMP-13, ADAMTS5, and cathepsin K in cartilage and MMP-3 and IL-1β in the synovial membrane. ELISA for plasma CTX-II. | Reduction in the depth and size of the lesions of the groups treated with SrRan, as well as the disorganization of the articular cartilage collagen networks. Reduction of subchondral bone plaque thickness in the group treated with SrRan 50 mg·kg⁻¹·d⁻¹. Decreased mRNA levels for MMP-1, MMP-13, and cathepsin K in the articular cartilage with SrRan 75 mg/kg/d. Decreased expression of IL-1β in the synovial... |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Model/Study Description</th>
<th>Treatment Details</th>
<th>Methods</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu et al, 2013</td>
<td>Sprague Dawley rats submitted to MMT in knee</td>
<td>4 groups with 32 animals each:</td>
<td>Histological analysis (OARSI), immunohistochemistry (TUNEL and SOX9), micro-CT, microspectroscopy and nanoindentation.</td>
<td>SrRan at a dose of 1800 mg/kg attenuated joint degeneration at week 6, improved apoptotic chondrocyte indexes, increased SOX9 expression, improved microstructural abnormality indexes and increased joint elasticity compared to MMT + saline group.</td>
</tr>
<tr>
<td>Tat et al, 2011</td>
<td>Culture of osteoblasts from subchondral bone samples</td>
<td>Culture media containing 0.1, 1 and 2 mM SrRan Control group with subchondral bone sample of patients without OA.</td>
<td>PCR for quantification of MMP-2, MMP-9, OPG, RANKL3 and RANKL1. Flow cytometry for RANKL membrane, ELISA for OPG and Western blot for MT1-MMP, ADAM17 and ADAM19.</td>
<td>Reduction of MMP-2 and MMP-9 expression and increased OPG synthesis and expression with concentrations of 1 and 2 mM SrRan. Elevation of RANKL levels and reduction of RANKL-3 isoform at 2 mM SrRan concentration. No effect on MT1-MMP and ADAM17 and ADAM19.</td>
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ACLT: Anterior cruciate ligament transection; ADAM: a disintegrin and metalloproteinase domain; ADAMTS5: a disintegrin and metalloproteinase with thrombospondin motifs; TMJ: temporomandibular joint; CINC-1: cytokine-induced neutrophil chemoattractant; CTX-II: C telopeptide of type II procollagen; ELISA: Enzyme linked immunosorbent assay; IL1β: interleukin 1 β; MIA: sodium monooiodoacetate; micro-CT: computed tomography; MMP: matrix metalloproteinases; MMT: medial meniscal tears; MT1-MMP: membrane type-1 matrix metalloproteinase; MV: Mechanical vibration; OARSI: Osteoarthritis research society international index; OPG: osteoprotegerin; OVX: oophorectomy; PCR: polymerase chain reaction; PET: paw elevation time; PO: per os; mRNA: Messenger RNA; RANKL: receptor activator of nuclear factor kappa-B ligand; SC: subcutaneous; SOX9: sex-determining region Y-box 9; TNF-α: tumor necrosis factor α; TUNEL: transferase-mediated dUTP-TMR nick end labeling assay.
Table S2. Clinical trials of use of strontium ranelate (SrRan) in osteoarthritis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Description</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEKOIA Trial</strong></td>
<td>Reginster et al, 2013 (40)</td>
<td>Multicenter placebo-controlled double-blind randomized clinical trial, initially with 1683 patients diagnosed with knee OA.</td>
<td>Three groups: -Placebo (n=559) -1 g/d SrRan (n=558) -2 g/d SrRan (n=559) Follow-up period: Three years</td>
<td>- Primary outcome: radiographic changes in relation to baseline. - Secondary outcomes: radioclinical progression, WOMAC score, visual analog scale, and urinary CTX-II levels. - Less radiological and radioclinical progression in users of SrRan. - WOMAC and pain scores were only lower with doses of 2 g/d over placebo. -CTX-II: lower levels with SrRan users - CPK transient increase</td>
</tr>
<tr>
<td><strong>SEKOIA post hoc analysis</strong></td>
<td>Pelletier et al, 2015 (42)</td>
<td>Of the 1683 patients with OA in the SEKOIA trial, a subgroup of 330 submitted to knee MRI at 12, 24, and 36 months of follow-up</td>
<td>Three groups of patients who performed MRI: -Placebo (n=113) -1 g/d SrRan (n=105) -2 g/d SrRan (n=112) Follow-up period: three years</td>
<td>- Primary outcome: changes in the global volume of cartilage in the knee and in the medial and lateral compartments in 36 months. - Secondary outcome: changes in bone marrow lesions associated with OA - Use of 2 g/d SrRan reduced the overall loss of cartilage volume in the tibial plateau at 12 and 36 months. -Medial compartment, doses of 1 g/d showed increased loss of cartilage. -Lateral compartment: 2 g/d of SrRan reduced cartilage volume loss in the tibial plateau from the first year of treatment, while 1 g/d doses reduced the loss after the second year of treatment. -Reduction of lesions in bone marrow with use of 1 g and 2 g/d of SrRan</td>
</tr>
<tr>
<td>Cooper et al, 2013 (43)</td>
<td>Analysis of radiological response to the treatment of SEKOIA trial patients.</td>
<td>Three groups: -Placebo (n=472) -1 g/d SrRan (n=445) -2 g/d SrRan (n=454) Follow-up period: three years</td>
<td>Identification of responders to the treatment in the criterion of reduction of the radiological progression of OA. Responders were divided into three levels of joint narrowing cut (≥ –0.1; –0.2; or –0.3 mm).</td>
<td>-For the three cuts of joint narrowing, there was a higher proportion of patients responding to SrRan 1g/d or 2g/d compared to placebo -NNT=13 for 1g/d and NNT=9 for 2g/d (for joint space reductions ≥ –0.3 mm).</td>
</tr>
<tr>
<td>Maheu et al, 2013 (44)</td>
<td>Of the patients included in the SEKOIA trial, 999 performed hand radiography to assess OA</td>
<td>Three groups: -Placebo (n=472) -1 g/d SrRan (n=445) -2 g/d SrRan (n=454) Follow-up period: three years</td>
<td>Secondary outcome of SEKOIA trial: radiographic and clinical evaluation of hand OA. Evaluation with radiological scores for hand OA (Kellgren-Lawrence; Kallman and Verbruggen) - Clinical evaluation by FIHOA and AUSCAN criteria.</td>
<td>-Discrete radiological progression of hand OA with placebo. No statistical difference for use of 1 g/d and 2 g/d. -Tendency to improve pain scores with use of SrRan 2 g/d, especially in patients with severe hand OA.</td>
</tr>
<tr>
<td>Bruyère et al, 2014 (45)</td>
<td>Analysis of treatment response of the 1683 patients with OA in the SEKOIA trial</td>
<td>Three groups: -Placebo (n=472) -1 g/d SrRan (n=445) -2 g/d SrRan (n=454) Follow-up period: three years</td>
<td>Identification of responders to treatment, based on WOMAC scores, OMERACT-OARSI index and MPCl and MCII criteria.</td>
<td>-There was no effect on symptoms at doses of 1 g/d over placebo - At doses of 2 g/d there was an improvement in the response to the WOMAC pain score. Response above the MPCI threshold in WOMAC for pain, stiffness, and physical function and above the MCII threshold for physical function.</td>
</tr>
<tr>
<td>Roubille et al, 2015 (50)</td>
<td>Of the 1683 patients with OA in the SEKOIA trial, a subgroup of 330 submitted to knee MRI at 12, 24, and 36 months of follow-up</td>
<td>Three groups of patients who performed MRI: -Placebo (n=113) -1 g/d SrRan (n=105) -2 g/d SrRan (n=112) Follow-up period: three years</td>
<td>Identification of meniscal extrusion or bone marrow lesion in the medial compartment of the knee.</td>
<td>Placebo group with more meniscal extrusion and/or bone marrow lesions, associated with greater reduction of joint space. Patients with 2 g/day had less loss of cartilage in cases of meniscal extrusion and/or bone marrow lesions.</td>
</tr>
</tbody>
</table>
Others
Bruyere et al, 2008 (38)  
*post hoc* analysis of patients in the TROPOS and SOTI trials who presented spine OA, in addition to osteoporosis.
1105 women with osteoporosis and spine OA (SOTI = 399 and TROPOS = 706) on 2 g/d of SrRan versus placebo for three years. Use of SrRan 2 g/d or placebo for three years.
Radiographic evaluation of narrowing of intervertebral lumbar spaces; presence of osteophytes and sclerosis. Low back pain (Likert scale in SOTI trial). Quality of life (SF-36).
Reduction of spinal OA progression with SrRan. Improvement of pain. No change in quality of life.

Alexandersen et al, 2010 (39)  
*post hoc* analysis of a randomized placebo-controlled study of 2617 postmenopausal women with osteoporosis who also had OA.

AUSCAN: Australian Canadian questionnaire; CPK: creatine phosphokinase; CTX-I: C telopeptide of type I procollagen; CTX-II: C telopeptide of type II procollagen; FIHOA: Functional index for hand osteoarthritis; MCII: minimal clinical important improvement; MPCI: minimal perceptible clinical improvement; NNT: number needed to treat; OA: osteoarthritis; OMERACT-OARSI: Outcome measures in rheumatology – Osteoarthritis research society international index; NMR: nuclear magnetic resonance; SEKOIA: Strontium ranelate efficacy in knee osteoarthritis trial; SF-36: Medical outcomes study-36 questionnaire; SOTI: Spinal osteoporosis therapeutic intervention trial; TROPOS: Treatment of peripheral osteoporosis trial; WOMAC: Western Ontario and McMaster Universities osteoarthritis index.

**Table S3.** Radiological progression of osteoarthritis with strontium ranelate treatment at different doses vs placebo (GRADE method).

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Certainty assessment</th>
<th># of patients</th>
<th>Effect</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirect evidence</td>
<td>Inaccuracy</td>
</tr>
<tr>
<td><strong>Treatment with 1 g of SrRan per day (follow-up: mean 36 months; evaluated with radiological progression)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reginster et al, 2013 (40)</td>
<td>randomized clinical trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Treatment with 2 g of SrRan per day (follow-up: median 36 months; evaluated with radiological progression)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Reginster et al, 2013 (40) Bruyere et al, 2008 (38)</td>
<td>randomized clinical trials</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

CI: Confidence interval; RR: Risk ratio.  
*The possibility of different phenotypes in osteoarthritis, suggesting that strontium ranelate might be more effective in certain subgroups of osteoarthritis patients, e.g., those with dominant subchondral bone changes.  
*Many patients had prior osteoporosis and spinal osteoarthritis, with no data on peripheral osteoarthritis being available.*