**Table S3**. Analysis of methodological bias in animal studies.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Studies**  **Signaling questions** | | **Leite et al. 2017** | | **Penitente et al. 2015** | | **Chumbinho et al. 2012** | | **Costa et al. 2010** | | **Leon et al. 2003** | |
| **1** | Was the allocation sequence adequately generated and applied? | | No | | No | | No | | ? | | No |
| **2** | Were the groups similar at baseline? | | Yes | | Yes | | Yes | | ? | | No |
| **3** | Was the allocation to the different groups adequately concealed during? | | ? | | ? | | ? | | ? | | ? |
| **4** | Were the animals randomly housed during the experiment? | | ? | | ? | | ? | | ? | | ? |
| **5** | Were the caregivers and/or investigators blinded from knowledge which intervention each animal  received during the experiment? | | No | | No | | No | | No | | No |
| **6** | Were animals selected at random for outcome assessment? | | ? | | ? | | ? | | ? | | ? |
| **7** | Was the outcome assessor blinded? | | ? | | No | | No | | No | | No |
| **8** | Were incomplete outcome data adequately addressed? | | ? | | ? | | ? | | ? | | Yes |
| **9** | Are reports of the study free of selective outcome reporting? | | Yes | | Yes | | Yes | | Yes | | Yes |
| **10** | Was the study apparently free of other problems that could result in high risk of bias? | | Yes | | Yes | | Yes | | Yes | | Yes |

Analysis of bias categorized by specific criteria of bias. Analysis of bias based on the SYRCLE tool(*BMC Medical Research Methodology* 14:43, 2014). Yes: low risk of bias; No: high risk of bias; ?: unclear risk of bias. It is not recommend calculating a summary score for each individual study when using this toll.

**Table S3**. Analysis of methodological bias in animal studies.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Selection bias 1** | **Selection bias 2** | **Selection bias 3** | **Performance bias 1** | **Performance bias 2** | **Detection bias 1** | **Detection bias 2** | **Attrition bias** | **Reporting bias** | **Other potential bias** |
| **Leite et al. 2017** | x | ✓ | ? | ? | x | ? | ? | ? | ✓ | x |
| **Penitente et al. 2015** | x | ✓ | ? | ? | x | ? | x | ? | ✓ | x |
| **Chumbinho et al. 2012** | x | ✓ | ? | ? | x | ? | x | ? | ✓ | x |
| **Costa et al. 2010** | ? | ? | ? | ? | x | ? | x | ? | ✓ | x |
| **Leon et al. 2003** | x | x | ? | ? | x | ? | x | ✓ | ✓ | x |

Analysis of bias categorized by domains. Based on the SYRCLE tool(*BMC Medical Research Methodology* 14:43, 2014). Selection bias 1: ✓= Adequate randomization; ?= randomized but no details; x=no evidence of randomization. Selection bias 2: ✓= Baseline characteristics given; ?= insufficient baseline characteristics; x= baseline characteristics not given. Selection bias 3: ✓= Evidence of adequate concealment of groups; ?= unknown of adequate concealment of groups; x= no evidence of adequate concealment of groups. Performance bias 1: ✓= Evidence of random housing of animals; ?= unknown housing arrangement. Performance bias 2: ✓= Evidence of caregivers blinded to intervention; x= no evidence of caregivers blinded to intervention. Detection bias 1: ✓= Evidence of random selection for assessment; ?= Random selection for assessment; x= no evidence of random selection for assessment. Detection bias 2: ✓= Evidence of assessor blinded; ?= unknown of assessor blinded x= no evidence of assessor blinded. Attrition bias: ✓= Explanation of missing animal data; ?= unknown of missing animal data; x=no explanation of missing animal data. Reporting bias: ✓= Free of selective reporting based on methods/results; ?= inconclusive reporting; x= selective reporting. Other potential bias: ✓=Free of other high bias risk; ?= insufficient data to determine risk of other bias.