Supporting Information

Safety and Toxicology of Magnolol and Honokiol
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Supplementary Methods

This review was conducted and reported in accordance with PICOS conceptual framework and the applicable features of the PRISMA guidelines [8,9].

1.1. Eligibility Criteria

- **Studies meeting the following criteria were considered for review:** (1) only original articles for different subtypes of observational studies, randomized controlled trials, case reports, animal studies, or *in vitro* studies; (2) pharmacokinetics and/or pharmacodynamics studies; (3) study population being humans both gender and any age, in case of animal studies mammalian animals were preferred; (4) intervention consisting of oral assumption of magnolia bark extract or its constituents, magnolol, and/or honokiol in case of safety evaluation and intra venous administration in case of ADME studies; (5) acute, short, subchronic, and long-term administration; (6) investigation of adverse or side effects as primary endpoint related consumption of magnolol, honokiol, or concentrated magnolia bark extract (more than 90% total magnolol plus honokiol).

- **Studies were excluded from the review if** (1) observed physiological/ pathological effects were due to the concomitant administration of magnolia bark extract and other herbal extracts or vitamins, minerals, probiotics, etc.; (2) other magnolia species besides *M. officinalis* were used for the investigation or if polyphenols different from magnolol and/or honokiol were analyzed; (3) studies analyzing synthetic derivatives of magnolol or honokiol; (4) studies focused on protective or positive effect of magnolia bark extract against different pathological conditions, as well therapeutic applications of magnolia bark extract or its constituents; (5) special delivery systems (e.g., microemulsions, micronization, nanoparticles, liposomes) that are not representative of the bioavailability of magnolia bark extract upon oral administration;
(6) articles having for object analytical chemistry and different techniques used to analyses magnolia bark extract; (7) nonpertinent studies regarding other subjects; (8) reviews; (9) commentaries, conference paper, meeting abstracts or nonoriginal articles; (10) magnolol plus honokiol percentage in magnolia bark extract was not specified or was less than 90%; (11) full-text articles were not in English.

1.2. Search Strategy and Study Selection

A computerized literature search was performed on May 2017 using eight online databases with international geographic coverage starting from 1910 up till present: AdisInsight Safety, Allied & Complementary Medicine, Biosis Toxicology, Embase, Global Health, International Pharmaceutical Abstracts, Medline, RTECS.

Title/abstract/keyword searches were made using Boolean search operators by ProQuest search engine: (magnolia bark extract OR houpu OR hou po OR magnolol OR honokiol OR magnolia p/o officinalis) AND (toxicology OR safe OR safety OR *toxicity OR tolerability OR LD50 OR NOAEL OR loa el OR feeding p/0 study OR organ p/0 damage OR tissue p/0 damage OR internal p/0 use OR overdose OR adverse p/0 reaction OR contraindication OR drug p/0 interaction OR risk p/0 group OR adverse p/0 effect OR Side p/0 effect OR secondary p/0 effect OR collateral p/0 effect OR undesirable p/0 effect OR rare p/0 effect OR rosiglitazone OR *glitazone OR PPAR* OR RXR OR metabolism OR absorption OR distribution OR excretion OR mutagen* OR genotox* OR genetic p/0 toxicity OR carcinogen* OR cancer OR tumour OR hyperplasia OR hypertrophy OR histology OR precancerous p/0 lesion OR paediatric OR pediatric OR malformation OR fetus OR birth p/0 rate OR natality OR multigeneration OR allerg* OR inflammation OR Ames OR “chromosome aberration assay” OR comet OR micronucleus OR micronuclei OR teratogen* OR pregnancy OR fertility OR lactation OR endocrine OR gonad* OR sperm* OR ovocyte* OR case p/0 report).
A total of 668 studies were identified from the eight databases after adjusting for duplicates. Additional 27 studies were obtained by hand search. In sum, 695 studies were identified and subsequently analyzed for eligibility criteria (see above) by title and/or abstract review. During screening, 633 studies were removed because not meeting eligibility criteria. The remaining 62 full-text studies were examined in detail, and in total, 44 studies were included for the systematic review (Fig. 2).