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Review

Danggui to *Angelica sinensis* root: Lost in translation? Are potential benefits of a TCM lost to European women? A review

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ABSTRACT

Q8 *Ethnopharmacological relevance:* Danggui (Chinese *Angelica* root; Dong quai; *Angelica sinensis* (Oliv.) Diels.) is a traditional Chinese herbal remedy with a long history of use in China, Korea and Japan. Even today it is still one of the herbs most commonly used by Traditional Chinese Medicine (TCM) practitioners in China, as well as Europe. It is mainly used for the treatment of women's reproductive problems, such as dysmenorrhea, amenorrhoea, menopause, among others. Using *Angelica sinensis* (Oliv.) Diels. root as the example, this Review examines the ease with which the use of a Traditional Chinese Herbal Remedy can be transposed from one culture to another. By examining the more recent literature, a number of aspects are considered by the author to be potentially *lost in translation*: (i) identity and quality (phytochemistry); (ii) tradition of use and processing (smoke-drying, stir-frying, with and without wine); (iii) method of use and traditional types of Chinese herbal medicines; (iv) ethnic differences (Caucasian vs. Asian); (v) efficacy, safety and potential for western drug–herb interactions. *Materials and methods:* This review is based on evaluation of the literature available in scientific journals, textbooks, electronic sources such as ScienceDirect, PubMed, Scopus, etc., as well as other web-sites. *Results:* A vast amount of information concerning the use of *Angelica sinensis* exists in the public domain. Many aspects associated with the use of the root are deemed problematical, such as identity, processing, amount and types of constituents, tradition of use in combination with other Chinese herbs, ethnicity of users, etc. Numerous constituents have been isolated with phthalides, ferulic acid and polysaccharides showing biological activities. *Conclusion:* In spite of the potential activities associated with the traditional use of danggui, and the many trials using the Chinese system of 'Zheng differentiation', well-designed western-style clinical trials carried out using the authenticated, chemically standardized crude drug material to confirm clinical efficacy are in short supply. However increasing research into *Angelica sinensis* extracts and constituents shows that many of the traditional uses are not without scientific basis.

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1. Introduction

Angelica sinensis (Oliv.) Diels. (Chinese Angelica root; danggui) has been used in China, Korea and Japan as a spice, tonic and medicine for more than a 1000 years and today is still one of the herbs most commonly used by Traditional Chinese Medicine (TCM) practitioners in China, as well as Europe (Williamson et al., 2013). It is recommended for anaemia, to promote blood circulation, relieve pain and treat constipation (Wu, 2005), but is used mainly for the treatment of women's reproductive problems, such as dysmenorrhoea, amenorrhoea and to 'enrich the blood' as an aid to recovery from blood loss after child birth or surgery. Danggui root can be used both as a 'medicinal food' cooked with meat and taken as soup or as a medicine, frequently combined with other herbs. A significant number of publications exist concerning its constituents and activities: *Angelica sinensis* 1426; Danggui 305; Dong quai 111 (<http://www.elsevier.com/online-tools/scopus>). Also numerous websites can be accessed advocating 'proprietary' TCM products containing danggui for relieving cramps, irregular menstrual cycles, infrequent periods, premenstrual syndrome (PMS) and menopausal symptoms. In addition there are many 'medical' websites, but these suggest caution as there is insufficient evidence of clinical efficacy.

As a traditional Chinese herbal medicine (TCHM) danggui was first recorded in European therapeutics circa 1899 and stated to be obtained from *Angelica anomala* var. *chinensis* (Read and Schmidt, 1923), a variety no longer recognised (<http://www.theplantlist.org>). It was marketed as 'EUMENOL' (Schneider, 1969) and was referred to in Merck's Annual Reports between 1899 and 1912 (Merck, 1899, 1912) as well as in the 16th Edition of The Extra Pharmacopoeia, Vol. I (Martindale and Westcott, 1915). It was reported to "exercise a favourable influence on menstrual problems even after 3 months". More recently the Working Party of the European Medicines Agency (EMA) Committee on Herbal Medicinal Products (HMPC) concluded that at present *Angelica sinensis* (Oliv.) Diels, radix does not comply with the EC Traditional Herbal Medicinal Product Directive (Directive 2004/24/EC) due to "(a) inadequate evidence allowing a demonstration of at least 30 years of medicinal use including at least 15 years in the European Union; (b) preliminary evidence of toxicological concerns in relation to the phytochemistry of the herbal preparations and (c) use needed the supervision of a medical practitioner" (EMA/HMPC/681574/, 2012).

Danggui is available as a food/dietary supplement in Europe as well as North America where it is known by the standardised

common name Dong quai (American Herbal Pharmacopoeia, 2003). Although a daily oral dose of 3 to 15 g of root is generally quoted, there appears to be no proven safe or effective dose for adults. Advertised doses vary ranging from one capsule (200 mg root powder + 50 mg root extract; 2:1) daily to one (530 mg root powder) or two capsules twice daily. Product standards also appear to vary (Zhao et al., 2013). With regard to suggested health claims in Europe for *Angelica sinensis* (AS), the European Food Safety Authority (EFSA) considered that there was insufficient evidence with regard to (i) maintenance of joints and (ii) oxygen transport at daily doses equivalent to 3–15 g of dried root or 3–6 g of powdered root (<http://www.efsa.europa.eu/en/efsajournal/doc/1281.pdf>).

2. Identity and quality—Lost in translation?

Botanically the source of Chinese angelica root is *Angelica sinensis* (Oliv.) Diels., with the synonym of *Angelica polymorpha* Maxim. var. *sinensis* Oliv. (<http://www.theplantlist.org>). It is recognised in China as 當歸; pinyin: danggui; in Japan as Toki, in Korea as Tangwi and as Tang-kuei in Taiwan. The plant is a perennial indigenous to China, Japan and Korea and belongs to the Apiaceae (Umbelliferae), a family rich in important culinary and medicinal plants, producing a variety of metabolites including flavonoids, polyacetylenes, sesquiterpenes, coumarins, phthalides, etc. Over 70 constituents have been identified in the roots of AS, including polysaccharides, ferulic acid, coniferyl ferulate, *Z*-ligustilide, *E*-3-butylidenephthalide and other phthalides (Lao et al., 2004; Yi et al., 2009; Chao and Lin, 2011; Fang et al., 2012; Jin et al., 2012). An essential oil can be distilled from the roots (0.2–0.65%) in which over 40 compounds have been identified (Sa et al., 2012), with the major constituents being *Z*-ligustilide (60–69%) and *E*-3-butylidenephthalide (6–10%) (Wedge et al., 2009). The main actives in the root are considered to be: (i) phthalides, (ii) organic acids and (iii) polysaccharides.

2.1. Substitutes for AS also called Danggui

Due to a large world-wide demand for Chinese angelica root, the following are common substitutes used in Japan and Korea (respectively *Angelica acutiloba* (Sieb. et. Zucc.) Kitag. and *Agylla gigas* Nakai). Though macroscopically similar, modern analytical methods allow for their identification, e.g. by the lower levels of

Z-ligustilide, ferulic acid and coniferyl ferulate (Lao et al., 2004; Lu et al., 2005a; Liang et al., 2010), as well the presence of coumarins. Xanthotoxin (8-methoxypsoralen) and isopimpinellin (5, 8-dimethoxypsoralen) are reported to be present in *Angelica acutiloba* (Katoh and Ninomiya, 2010) and 9 coumarins, including marmesin, lomatin and decursin that are found in *Agylla gigas* (Kim et al., 2006; Ahn et al., 2008). Coumarins are absent in *Angelica sinensis* root according to (Zschocke et al., 1998; Kim et al., 2006; Wedge et al., 2009) but archangelicin, isoimperatorin and osthuthol are listed as being present according to the EMEA/HMPC (2006). There appears to be considerable ambiguity not only about the coumarins in the volatile fractions of roots from *Angelica* species (Kim et al., 2006), but also about the types and amounts of terpenes (EMEA/HMPC, 2006; EFSA/SC/COMP, 2007; Wedge et al., 2009), questioning the source of danggui used in the analyses. Such ambiguities should in the future be reduced by the recent publication of "A Good Practice Handbook for Scientific Publications on TCM" (Chan et al., 2012).

2.2. Variation of constituents in AS

Considerable variation in concentrations of active constituents have been reported, both for the essential oil (0.4–0.7%) and ligustilide (0.5–5.0%) (WHO, 2004). The reported amounts of the constituents of AS are known to vary depending on (i) time of year (Sa et al., 2012; Qian et al., 2013), (ii) site of collection (Lao et al., 2004; Deng et al., 2005; Wang et al., 2013; Zhang et al., 2013), (iii) plant part, i.e. whole root, root head, rootlet, root slice (Lu et al., 2005b), (iv) extraction procedure (Lao et al., 2004; Lu et al., 2004, 2005a, 2009; Deng et al., 2005; Kim et al., 2006; Huang et al., 2008) and (v) method of analysis (Zschocke et al., 1998; Lao et al., 2004; Deng et al., 2005; Lu et al., 2005a,b; Kim et al., 2006). For standardization and use in Chinese Materia Medica *Angelica sinensis* is collected in late autumn, after 2 years of cultivation, (mainly in Gansu Province of NW China) and smoke-dried over low heat after the rootlets are removed (Wu, 2005). From the monographs cited below, it is apparent that there are significant differences between the standards applied to Chinese and European *Angelica sinensis* root.

<i>Angelica sinensis</i> Root B.P. for use in THM (B.P. 2012: British Pharmacopoeia, 2012)	Dried whole root of <i>Angelica sinensis</i> (Oliv.) Diels. (<i>Angelica polymorpha</i> Maxim. var. <i>sinensis</i> Oliv.). The dried root consists of the top (uppermost part), main body and small lateral roots (tails). It is collected in late autumn, removed from rootlets and dried	Not less than 0.1% of Z-ligustilide (C ₁₂ H ₁₄ O ₂), calculated with reference to the dried material.
Processed <i>Angelica sinensis</i> Root B.P. for use in THMP (B.P. 2012: British Pharmacopoeia, 2012)	Smoke-dried, whole or fragmented root, with rootlets removed, of <i>Angelica sinensis</i> (Oliv.) Diels collected in late autumn	Minimum 0.050 per cent of <i>trans</i> -ferulic acid (C ₁₀ H ₁₀ O ₄ ; M _r 194.2)
<i>Angelica sinensis</i> Root Ph.Eur. (European 2012)	Smoke-dried, whole or fragmented root, with rootlets removed, of <i>Angelica</i>	Minimum 0.050 per cent of <i>trans</i> -ferulic acid

Pharmacopoeia 7th ed., 2012)	<i>sinensis</i> (Oliv.) Diels collected in late autumn	(C ₁₀ H ₁₀ O ₄ ; M _r 194.2)
Angelicae Sinensis Radix (Danggui) P.P.R.C. (Chinese Pharmacopoeia Commission, 2010)	The dried root of <i>Angelica sinensis</i> (Oliv.) Diels (Fam. Umbelliferae). The drug is collected in late autumn, removed from rootlet and soil, slightly dried and tied up in small bundles, placed on a shelf and smoke dried	Not less than 0.4% volatile oil and not less than 0.05% of ferulic acid (based on dried drug)
Radix Angelicae Sinensis, (Chinese Medicine Division, Government of Hong Kong (cmd.gov.hk))	The dried root of <i>Angelica sinensis</i> (Oliv.) Diels (Fam. Apiaceae). The root is generally collected in late autumn after 2 years of plantation. The stems, leaf sheaths, rootlets and soil removed, slightly dried and tied up in small bundles, then placed on a shelf and smoke-dried	Not less than 0.60% of Z-ligustilide (C ₁₂ H ₁₄ O ₂) calculated with reference to the dried material

There appears also to be ambiguity in the meaning of 'processed' between the Chinese and European monographs. *Angelica sinensis* Root B.P. for T.H.M. for example is not smoke-dried, but Processed *Angelica sinensis* Root B.P. is. In contrast in the Chinese Pharmacopoeia (PPRC 2010) monograph 'Processing' of *Angelicae Sinensis Radix* indicates "eliminate foreign matter, wash clean, soften thoroughly, cut into thin slices, and dry in the sun or at a lower temperature". The Chinese smoke-dried roots are richer in ligustilide than their European counterparts (> 0.4% volatile oil contains circa 0.25% ligustilide PPRC and 0.6% in Hong Kong vs. 0.1% in B.P. and Ph. Eur.). 'Smoking' can also refer to fumigation with sulfur dioxide, although the Chinese Pharmacopoeia does not specifically mention this as an acceptable drying method (Sturgeon, 2013).

2.3. Active constituents

2.3.1. Phthalides

Numerous phthalide derivatives have been isolated from 9 *Angelica* species. A comprehensive list is found in Lin et al. (2005) as well other references (Lao et al., 2004; Lu et al., 2006; Ting Kan et al., 2008; Lü et al., 2009; Wedge et al., 2009; Tang et al., 2010b; Chao and Lin, 2011; Zhong et al., 2011; Yeh et al., 2012). The major constituent is Z-ligustilide (61–69% in the essential oil), with other phthalides such as *E*-ligustilide, Z-butylidene-phthalide, 3-butylphthalide, 3-butylidene-4-hydroxy-phthalide, senkyunolide A, 6,7-epoxyligustilide, senkyunolide F, senkyunolide H, senkyunolide I, 6,7-dihydroxylicustilide and phthalide dimers including riligustilide, levistolide A and senkyunolide O (Lü et al., 2009). Many of these are also present in Chuanxiong Rhizoma (*Ligusticum chuanxiong* Hort.; syn. *Ligusticum wallichii*), (Yan et al., 2008; Kim and Rhyu, 2010a; Kim et al., 2010b; Ran et al., 2011; Li et al., 2012) a TCHM frequently combined with *Angelicae Sinensis Radix* (Hou et al., 2004; Tang et al., 2006). Results of Korean research has found that the

combination of *Ligusticum wallichii* (LS) and *Angelica gigas* (AG) elicited a synergistic effect on vasorelaxation in isolated rat aortas and antihypertension in spontaneously hypertensive rats, with the 1:1 ratio of LS:AG being the most effective of all combinations tested (Kim and Rhyu, 2010a).

Extensive investigations have been carried out and published on the biological activities of ligustilide, including inhibition of uterine contractions (Du et al., 2006; Tang et al., 2010b), vasodilation (Chan et al., 2007), decrease in platelet aggregation (Zhang et al., 2009b), analgesic (Du et al., 2007) and anti-inflammatory effects (Saw et al., 2013), attenuation of lipopolysaccharide-induced pro-inflammatory response (Wang et al., 2010) and endotoxin shock (Wang et al., 2006; Shao et al., 2011). Ligustilide is stated to be neuroprotective (Wu et al., 2011), to inhibit vascular smooth muscle cells proliferation (Lu et al., 2006), to be antidepressant and serotonergic (Zhou et al., 2012) and a novel transient receptor potential cation channel (TRPA1)-activator (Zhong et al., 2011). *N*-butylidenephthalide inhibits angiogenesis in vitro and in vivo (Yeh et al., 2011) and endothelial sprouting (Yeh et al., 2012). The pharmacokinetics of ligustilide in humans are little understood, but animal studies have found that after oral administration < 3% of ligustilide was absorbed at only the highest dose (500 mg/kg) and rapidly eliminated (Yan et al., 2008). The main metabolic reactions of phthalides appear to be conjugation with glutathione, cysteine, glucuronic and sulfuric acids (Zuo et al., 2011).

2.3.2. Ferulic acid and coniferyl ferulate

The activity of processed *Angelica sinensis* root is also linked to the ferulic acid (FA) content (Chinese Pharmacopoeia, 2010; B.P. 2012: British Pharmacopoeia, 2012; European Pharmacopoeia 7th ed., 2012). This content varies significantly depending on the methods of extraction and analyses (Lu et al., 2005b; Sun et al., 2006; Xie et al., 2009). FA rarely occurs freely in plants but more usually as its unstable ester coniferyl ferulate which has actions similar to FA, but stronger (Lu et al., 2005b). Ferulic acid is stated to possess numerous bioactivities mostly associated with its antioxidant and radical scavenging activities (Kikuzaki et al., 2002). These effects include anti-inflammatory (Ozaki, 1992), antithrombotic, anticoagulant and cardioprotective (Wang and Ou-Yang, 2005), neuroprotective after cerebral ischaemia (Cheng et al., 2008a, 2008b), radioprotective by inhibiting of gamma radiation-induced DNA strand breaks (Maurya and Devasagayam, 2013) and inhibitory of oxytocin-induced mouse uterine contraction in vitro (Yu et al., 2009). Results in humans show that after oral ingestion peak plasma concentrations of FA were reached within 1 h and declined over 24 h (Xiao et al., 2009). The peak time for maximal urinary excretion was approximately 7 h and the recovery in the urine, on the basis of total free ferulic acid and feruloyl glucuronide excreted, was 11–25% of that ingested (Bourne and Rice-Evans, 1998).

2.3.3. Polysaccharides

Interest in the bioactivities of polysaccharides isolated from AS has recently increased (Chao and Lin, 2011; Jin et al., 2012). Chemically polysaccharides isolated from fresh roots are reported to consist of uronic acid [8.6%] and the sugars rhamnose, arabinose, mannose, glucose and galactose [molar ratio of 1.00: 4.54: 2.98: 11.09: 7.45] (Yang et al., 2006). A polysaccharide extracted from dried, defatted *Angelica sinensis* roots was determined to have a molecular weight of 78 kDa and to consist of 95% sugars, mainly arabinose, glucose and galactose [molar ratio 1: 5.68: 3.91] (Liu et al., 2012), while two homogenous polysaccharides: APS-1a contains the sugars galactose, arabinose and glucose [molar % of 57.35: 27.67: 14.98] and APS-3a, galactose, arabinose and glucose

[molar % of 84.54: 6.50: 8.98] (Zhao et al., 2012). Several acidic polysaccharides (Yang et al., 2008a; Lee et al., 2012) have also been isolated and fractionated, with different fractions showing varying activities (Cao et al., 2010a).

In common with other plant-derived high molecular weight polysaccharides (Lemmon et al., 2012), those from AS have been shown to have immunomodulatory actions (Yang et al., 2006, 2008a, 2008b; Sun et al., 2010). In addition they are reported to be antioxidant (Yu et al., 2013; Ai et al., 2013), myeloprotective (Lee et al., 2012), cardioprotective (Zhang et al., 2010), have antitumour (Cao et al., 2006, 2010a, 2010b) and analgesic effects (Song et al., 2009) and promote proteoglycan synthesis by chondrocytes which is of potential relevance to osteoarthritis (Qin et al., 2013). Some fractions have been reported to have thrombopoietic (Liu et al., 2010b) and haematopoietic properties (Liu et al., 2010a; Lee et al., 2012) by inhibiting hepcidin expression (Wang et al., 2011; Zhang et al., 2012b) suggesting their use for treating iron deficiency anaemia (Liu et al., 2012), while APS-1a and -3a could be used as radioprotective agents for promoting bone marrow haematopoiesis (Zhao et al., 2012). Hepatoprotective and antidiabetic activities have also been suggested (Jin et al., 2012).

3. Processing—Lost in translation?

“Processing refers to any treatment (such as cutting, washing, stir-frying, drying, burying) which transforms raw herbs into Chinese Materia Medica, e.g. to enhance efficacy, reduce toxicity, etc.” (Zhao et al., 2010). Danggui root can be used in numerous ways: with or without heat, as an aqueous extract in soup or tea, sprayed with alcohol or as a tincture. It can be smoke-dried (Chinese Pharmacopoeia, 2010; B.P. 2012: British Pharmacopoeia, 2012; European Pharmacopoeia 7th ed., 2012), used whole or sliced, fresh or dry, fried, baked or charred, with or without wine (American Herbal Pharmacopoeia, 2003; Bensky et al., 2004; Tang et al., 2010a; Zhao et al., 2010; Luo et al., 2012) or as the essential oil. Any modification to the root material, extraction solvent, processing times and temperatures will alter the metabolite profiles and thereby the flavour and biological activities (Huang et al., 2008). For example during air oxidation of the root ligustilide aromatizes to dehydroligustilide which has a different activity profile (Zhong et al., 2011). Also the alkylphthalides being volatile, highly unstable and polar (Schinkovitz et al., 2008) will be present in lower concentrations in aqueous extracts prepared using heat (Huang et al., 2008; Xie et al., 2009; Zheng et al., 2010b) as will the heat-labile coniferyl ferulate.

These different processing methods will affect the actions of the final preparation. Traditionally these are for *Angelicae Sinensis Radix* (ASR)—used to enrich blood, regulate menstruation, regulate bowels; *Angelicae Sinensis Radix* stir-fried with wine—used to activate blood circulation and stimulate menstrual discharge; Charred *Angelicae Sinensis Radix*—to arrest bleeding (Zhao et al., 2010). These traditions have recently been confirmed by research which found that using the optimized conditions of processing ASR with wine (heating in an oven at 80 °C for 90 min with flipping twice per hour), the solubilities of ferulic acid and Z-ligustilide from ASR were markedly increased and decreased, respectively. In parallel, the biological functions of processed ASR were enhanced in both anti-platelet aggregation and estrogenic activation (Zhan et al., 2011).

3.1. Decoctions

Decoctions are the easiest and most traditional way to prepare a Chinese herbal prescription, with the method involving heating in water for a specified period, straining and taking the extract 2 or 3 times a day (Williams, 2003). Analysis of a decoction of danggui,

showed Z-ligustilide was present in low concentration (0.055%), while Z- and E-butylidenephthalide, as well as coniferyl ferulate, were not detectable (Xie et al., 2009). Higher concentrations occurred in extracts after a short-heat (30 min) with 20% aqueous ethanol (Huang et al., 2008). Phenolic acids being water soluble will be present in higher concentrations in aqueous extracts. Also the unstable coniferyl ferulate will be readily hydrolysed during extraction to ferulic acid (Lu et al., 2005b; Xie et al., 2009). An enhanced ferulic acid content would affect the activity of the preparation, e.g. by enhancing the membrane permeability of and increasing the absorption of flavonoids, such as formononetin and calycosin from Astragali Radix when used in combination with Angelicae Sinensis Radix (Zheng et al., 2012).

Different processing methods have also been found to affect contents of the water soluble polysaccharides (Lv et al., 2011), their thermal stability and bioactivity (Yang et al., 2008a). Heating to 90–150 °C, as well as for 6 to 12 h at 80 °C were found to cause significant chemical changes to the polysaccharides (Yang et al., 2008b). For brain antioxidant activity optimal extraction conditions were determined as: extraction time 180 min, water/solid ratio of 6, extraction temperature 100 °C (Ai et al., 2013), but for hepatoprotective activity optimum polysaccharide yield (5.6%) and extraction was considered to be boiling in water for 130 min and using a water/solid ratio of 5 (Yu et al., 2013).

Decoctions have some disadvantages, e.g. with regard to quality control, stability and the requirement of having to consume large volumes of 'nasty-tasting' liquid. Granules (e.g. *Angelica sinensis* 10:1 concentrated granules) are now being developed to overcome these problems, but whether they have equivalence with decoctions remains to be determined (Luo et al., 2012).

3.2. Stir-baking or stir-frying with and without wine

Rice wine is typically used to process Chinese herbs and has an alcohol content of 18–25%. The contents of volatile compounds (ligustilide, butylidenephthalide and butylphthalide) were found to be much higher in the 20% ethanol extracts than aqueous extracts. Boiling the *Angelica sinensis* root slices in 20% ethanol for 30 min was the optimum extraction period for flavour and antioxidant activity (Huang et al., 2008). A recent report where AS root was 'stir-baked' with wine (i.e. sprayed with wine and placed in an oven at 80° for 90 min, flipping twice per hour) found higher levels of ferulic acid and lower levels of ligustilide than the crude drug (Zhan et al., 2011, 2013). Stir-fry processing without wine found high levels of Z-ligustilide and ferulic acid to be lost within 30 min of cooking, with levels of 5-hydroxymethylfurfural and 5-hydroxymaltol increasing. Aqueous extracts of these stir-fry-processed danggui were found to show antihypertensive effects (Zhou et al., 2013). Such changes in metabolite concentrations probably explain modifications in activity due to processing and of herbal combinations containing *Angelica sinensis*, such as Si Wu Tang (Zhan et al., 2013) and Danggui Buxue Tang (Zheng et al., 2010b; Zhang et al., 2012a).

3.3. Sulfur fumigation

Sulfur fumigation processing (also known as 'smoking') is being used as a shorter alternative drying method for TCM herbs, potentially reducing pests and microbial contamination and improving their shelf-life, but having detrimental effects on the safety and quality of TCM herbs, by altering their chemical profiles, pharmacokinetics and bioactivities (Kan et al., 2011). For example the sulfur-fumigation process has been found to cause significant losses of the main active constituents (steroidal alkaloids) of *Fritillaria thunbergii* bulbs (Zhebeimu) (Duan et al., 2012) and the furocoumarins in *Angelica dahurica* root (Baizhi) (Wang et al.,

2009a). Comparison of sun-dried and sulfur-fumigated *Angelica sinensis* extracts showed significant reduction of constituents in both aqueous and alcoholic extracts, with a new compound appearing in the alcoholic extract (Lou et al., 2012). Sulfur-fumigated roots also showed increased levels of heavy metals (Lou et al., 2013). Though not officially referred to in Pharmacopoeias, sulfur-processed danggui is commercially available (American Herbal Pharmacopoeia, 2003).

4. Traditional systems in Chinese herbal medicine—Lost in translation?

Chinese and Western medicine differ with regard to diagnosis, treatment and prevention of disease. Chinese medicine uses a holistic approach addressing the person's entire constitution. It is based on concepts anchored in a long history of use and practice and cannot be totally explained scientifically. TCM prescriptions consisting of herbs, animal parts and/or minerals, are usually tailored to the individual patient. In contrast Western medicine diagnosis is specific to disease and symptoms, has a relatively shorter history of use and is based on clinical/scientific evidence. Treatments use drugs that are chemical entities with distinct pharmacological activities.

4.1. Herbal practitioner

The practitioner requires a license to practice and has the most understanding and training with regard to disease diagnosis and treatment. Health in the Chinese tradition is perceived as a harmonious interaction of the outside world with entities that regulate digestion, breathing, aging, etc. Disease is interpreted as a disharmony in interaction. The diagnostic and therapeutic methods of TCM practice are based on pattern classification, also called syndrome or ZHENG differentiation (Su, 2013), and relate symptoms to patterns of an underlying disharmony, mainly by palpating the pulse and inspecting the tongue. In TCM the practitioner uses different methods, including acupuncture and herbs, to treat various conditions. The prescriptions (herbal combinations of varying complexity and preparation methods) then issued by the practitioner are tailored to the individual patients (*personalised medicine*). In contrast, herbal medicine in 'western' countries usually use 'simples', i.e. products containing a single ingredient. Increasingly however, in modern TCM research syndrome differentiation is becoming integrated with orthodox medical diagnosis, for example in the areas of menopause (Rampp et al., 2008), primary dysmenorrhoea (Zhu et al., 2009) and rheumatoid arthritis (Zhang et al., 2012c). Such research in the future should lead to more clearly designed clinical trials and create a more accurate evaluation and translation of the use of traditional Chinese medicines into western practice (Flower et al., 2012; Jiang et al., 2012; Lu et al., 2012). Development of new modern analytical techniques will also allow for the simultaneous investigation of herbal drug interactions and therapeutic monitoring, leading to a better understanding of the complex mechanisms of absorption, distribution, metabolism, excretion and safety of Chinese herbal combinations such as *Rhizoma Chuanxiong* and *Angelica sinensis* (Zeng et al., 2014).

4.2. Pre-prepared formulations

These are one step removed from the TCM practitioner and are ready-made combinations of herbs available to the general public to treat certain conditions without reference to a complete system of medicine. One company alone manufactures 280 of these formulations, designed for specific indications. Of these, 71 contain

danggui. Some of the herbs are traditionally put together ('Classic Pairs'), such Danggui and Chuanxiong Rhizoma (*Ligusticum chuanxiong*) or Danggui and Radix Astragali membranacei (*Astragalus membranaceus*) or 'Standard Combinations' (*American Herbal Pharmacopoeia*, 2003; Wu, 2005). Two of the most popular formulations for Women's Health are:-

Si Wu Tang (four substance decoction) (Gou et al., 2003; Jia et al., 2005; Rowlands et al., 2009; Wang et al., 2009b; Tang et al., 2010b; Chang et al., 2013) formulated with varying ratios of Radix Angelicae Sinensis (dang gui), Radix Rehmanniae (shu di huang), Radix Paeoniae Alba (bai shao yao) and Rhizoma Ligustici (chuan xiong). It is traditionally used as a decoction. Its function is to tonify and activate blood, smooth the liver and regulate menstruation (*American Herbal Pharmacopoeia*, 2003).

Danggui Buxue Tang is available in various formulations (Gao et al., 2007a, 2007b; Xie et al., 2012; Zhang et al., 2012; Zheng et al., 2012) ranging from the TCM 'Drug Pair' Radix Angelicae Sinensis (ASR) and Radix Astragali (AR) in a ratio of 5:1 to a more complex combination with Fructus Jujubae (JF), Rhizoma Zingiberis Recens (RZR). Traditionally it is prepared as an aqueous decoction after boiling twice in water for 2 h (Zheng et al., 2012). Its suggested use for gynaecological disorders such as anaemia, infertility, has proved to be of potential for the perimenopause (Xie et al., 2012) and menopause (Gao et al., 2007b; Haines et al., 2008). Recipe ASR:AR (5:1) has proved to be the optimum ratio for erythropoietin expression (Gao et al., 2008; Zheng et al., 2010a), immunomodulatory, osteotropic and oestrogenic effects (Gao et al., 2007a). This herbal decoction is potentially of value in treating osteoporosis (Choi et al., 2011).

Danggui Ji Hwang Yeum, a combination of Radix Angelicae Sinensis, Rhizoma Rehmanniae, Radix Dioscoreae and Cortex Eucommiae, is another oriental prescription used for the management of osteoporotic disorders and has been found effective in preventing bone loss in ovariectomized rats (Chae et al., 2004).

4.3. Chinese patent remedies

These are furthest away from the TCM practitioner and are preparations in finished dosage form containing herbs, animal parts and/or minerals. They are inexpensive and widely available through on-line retail websites and probably have valid biological activity. For example Bak Foong Pills (BFP) is a patent remedy with a long history for treating gynaecological disorders (Gou et al., 2003). The formulation contains, among other things, 26 herbal ingredients including: *Phellodendron amurense* (huāng bō), *Corydalis yanhusuo* (yan hu suo), *Ligusticum wallichii* (Chuan xiong), *Panax ginseng* (Renshen), *Glycyrrhiza uralensis* (gān cǎo) and *Angelica sinensis* (Danggui). *Phellodendron amurense* was found to be a potent uterine muscle relaxant following oxytocin-induced contractions ex-vivo, an effect which could explain the alleviation by BFP of menstrual pain (Rowlands et al., 2009). In vitro results suggest anti-apoptotic activity and potential in treating neurodegenerative diseases (Jia et al., 2005). *Ligusticum wallichii*, used in TCM for cardiovascular and cerebrovascular effects (Yan et al., 2008; Li et al., 2012; Wang et al., 2012) was found to induce vasorelaxation in isolated rat aorta (Kim et al., 2010b). An ethanolic extract (70%) of BFP, more so than an aqueous extract, significantly inhibited in vitro platelet aggregation and prolonged bleeding times in vivo (Gou et al., 2003). Although freely available these preparations may carry misleading advertising, be of dubious quality or be contaminated with excessive levels of heavy metals and orthodox drugs (Kang-Yum and Oransky, 1992; Chan, 2003). Excessive levels of mercury were recently found in batches of Bak Foong Pills (<http://www.mhra.gov.uk>). Excessive levels of pesticides also pose a risk (Wan et al., 2010), for example high

levels of phorate were recently found in samples of *Angelica sinensis* (<http://pested.ifas.ufl.edu/newsletters/2013-08/herbal.html>).

5. Ethnic differences—Lost in translation?

One of the most important sources of variability in drug metabolism is genetic variability in drug-metabolizing enzymes (Yasuda et al., 2008). Environmental factors (diet, nutrition, climate, life style) also can lead to ethnic differences in drug metabolism, which in turn will affect drug dosage, dosage regimen, safety and efficacy. Differences in metabolism between East Asians and Caucasians are common especially in the activity of several cytochrome P450 enzymes. Ethnic origin and gender are also associated with cultural attitudes towards health and disease.

5.1. Predisposition to disease

A few studies have demonstrated that interactions between diet and gene variants mediate the risk of chronic disease (Simopoulos, 2008; Merino et al., 2010). Chinese/Asian and European ancestries have been proved to be genetically distinct (Phillips et al., 2013) and gene differences combined with lifestyle and diet create ethnicity. Environmental factors, as well as diet, interact with ethnic differences (Brenner et al., 2011), creating a predisposition to non-communicable diseases such as Parkinson's (Nauert, 2007), diabetes and cardiovascular disease (Sergey et al., 2011) and osteoporosis (Lei et al., 2006). The latter could be related to a low calcium intake by the general Chinese population increasing the risk of osteoporosis (Woo et al., 1998). In Northern China for example, not only was calcium intake low and the vitamin D status poor, but higher parathyroid hormone concentrations were found when compared to their British counterparts (Yan et al., 2009). Dietary intake can also create different plasma proteins which can be used as biomarkers of disease. For example the pro-inflammatory Principal Component 3 is positively associated with the eastern dietary pattern and high in south Asians vs. Principal Component 1 which is positively associated with a western dietary pattern and is low in east and south Asians (Garcia-Bailo et al., 2012).

The dietary balance of omega-6/omega-3 fatty acids is an important risk factor for coronary heart disease, with high omega-6 and low omega-3 fatty acid intake promoting many chronic inflammatory diseases such as cardiovascular disease (Simopoulos, 2008). Genetic polymorphisms control the metabolism of omega-6 and omega-3 fatty acids and cytokines related to inflammation (Simopoulos, 2010; Zhou et al., 2010). Cardiovascular disease (CVD) is one of the most common chronic diseases in China (Yang et al., 2013) and more Asians with diabetes (77%) die from circulatory disease than Europeans (46%) (Mather et al., 1998). The Ala allele (protective against diabetic retinopathy in type 2 diabetes) is detected in only 1% of Chinese compared with 12% in Caucasians (Ma et al., 2012). Many diets of Chinese women, especially during pregnancy, also have this high omega-6/omega-3 ratio with poor marine omega-3 intake, creating problems in neonates (Zhang et al., 2009a) and increasing the risk of breast cancer (Simopoulos, 2010; Murff et al., 2011). A predisposition to develop early onset (< 40 years) breast cancer is higher in Chinese women (20%) than in White American women (6%) (Chen et al., 2012b). Constituents of *Angelica sinensis* have been found to exert anti-cancer, anti-inflammatory and anti-cardiovascular effects (Chao and Lin, 2011).

5.2. Female reproductive and uterine complaints

Danggui is an herbal medicine traditionally used by women of Chinese ancestry being advocated for women's reproductive problems such as primary dysmenorrhea (period pains) and menopausal symptoms. Pain is a subjective experience with multiple dimensions, such as culture (Clark Callister, 2003), gender (Soetanto et al., 2006; Racine et al., 2012) and ethnicity. The perceived pain barriers of Asian patients were found to be different to those of Western patients (Chen et al., 2012a) and pain tolerance was different in Asian compared to White women (Woodrow et al., 1972). The menstrual cycle also appears different between Caucasian and Chinese women. Menstrual pain for example was found to start prior to the menstrual period and was more intense in Australian women, while in Chinese women pain started on the first day and was less intense (Zhu et al., 2009, 2010). Also the menstrual cycle length was found to be significantly longer in Asian vs. Caucasian women (Liu et al., 2004) and the menstrual bleed was significantly heavier in Chinese vs. Caucasian women (Goldman et al., 2012). Women with polycystic ovary syndrome (PCOS) and oligo/amenorrhoea showed Chinese to have lower systolic and diastolic blood pressure, higher incidence of amenorrhoea (74%) and hyperandrogenism (92%) than Dutch Caucasian women (27% and 64%, respectively) (Guo et al., 2012).

A large multiethnic study into factors associated with age at natural menopause concluded that possibly genetic and environmental factors were involved (Gold et al., 2001). For example vasomotor symptoms associated with menopause (e.g. hot flashes) appeared to be less prevalent in Chinese vs. Caucasian women (Ho et al., 1999) and both somatic and psychological symptoms were suffered less by Asian women (Rahman et al., 2010). Significant differences between German and Chinese women regarding menopausal symptoms (based on Kupperman-Index) were found using a combination of TCM diagnosis and hormone status. German women showed a higher prevalence of formication and depression and had lower levels of testosterone, compared to Chinese women who experienced more vertigo, headache and paraesthesia (Rampp et al., 2008). The 6- β -hydroxycortisol/cortisol ratios were found to vary during menstrual cycles and in Asian women the ratios are 2–3 times lower than in Caucasians (Lin et al., 1999). These ethnic differences between Asians and Caucasians could be related to the mechanisms regulating hepatic CYP3A expression, a family of enzymes associated with the metabolism and synthesis of cholesterol, steroids and other lipids (Yamaori et al., 2005).

5.3. Pharmacogenomics/pharmacogenetics

The identification of genetic variation, expression and function, together with the hereditary response to drugs are subjects of increasing importance that may help explain different responses by Chinese and other ethnic groups to TCHMs and drugs (Lou 1990; Li et al., 2007). Of major importance are the cytochrome P450 (CYP) family of liver enzymes, responsible for breaking down more than 30 different classes of drugs. DNA variations in genes that code for these enzymes can influence their ability to metabolize certain drugs. Less active or inactive forms of CYP enzymes that are unable to break down and efficiently eliminate drugs from the body can cause drug overdose in patients. Many dietary constituents can induce or inhibit cytochrome P450 enzymes. Flavonoids for example, inhibit CYP1A1 and 1A2, enzymes which exhibit genetic polymorphisms and could be involved in cancer development, e.g. aristolochic acid nephropathy (syn. Chinese herbs nephropathy) (Tanaka et al., 2001; Stiborova et al., 2012). Reduced CYP2A6 activity may also affect lung cancer risk, since

CYP2A6 is involved in the metabolic activation of several carcinogens, some of which are specific to lung cancer. Ethnic differences in nicotine metabolism have been related to variations in CYP2A6 activity which investigators found to be lower in Chinese-Americans than in White people (Nakajima et al., 2006).

The major isoenzymes involved in the in vitro metabolism of ligustilide are CYP1A2, CYP2C9 and CYP3A4 (Qian et al., 2009). Water and ethanol extracts of *Angelica sinensis* have been shown to affect steroid hormone-regulated gene expression (Rosenberg Zand et al., 2001), increase rat liver CYP3A4 and CYP2D6 activities (Tang et al., 2006). East Asians are poor metabolizers of CYP2D6. Drug pharmacokinetics (plasma clearance) of CYP2D6 and CYP2C lipophilic substrates are lower in Chinese (Kim et al., 2004). The development of early onset (< 40 years) breast cancer is higher in Chinese women (20%) than in White American women (6%) (Chen et al., 2012a). A possible explanation of this predisposition could be the metabolism of arachidonic acid by CYP2C19 to biologically active epoxy-eicosatrienoic acids, which significantly promotes proliferation of cancer cells in vitro and in vivo.

Warfarin is a commonly used oral anticoagulant with a narrow therapeutic range and large variation in individual dosage requirements. Genetic variations are known to influence warfarin dosage with Chinese requiring lower doses than Caucasians, e.g. the warfarin maintenance dose: Chinese (3.3 ± 1.4 mg/day) vs. Caucasians (4–6 mg/day); with heart disease Japanese (3.3 mg/day) vs. American Caucasians (4.9 mg/day) (Kim et al., 2004; Johnson, 2008). Differences in the allelic frequencies of two genes CYP2C9 and vitamin K epoxide reductase complex 1 (VKORC1) largely explain the difference in warfarin requirements, but still leave 26% of dose variability unaccounted for (Lam and Cheung, 2011). Also used to prevent thromboembolic events are oral anti-platelet agents such as prasugrel and clopidogrel. These are thienopyridines prodrugs that are converted in vivo to active metabolites, which bind irreversibly to and inactivate P2Y₁₂ receptors. Hepatic cytochrome P450 isoenzymes CYP3A4, CYP2C9, CYP2C19 and CYP2B6 are involved in their metabolism. Healthy Chinese appear to respond differently to treatment with these drugs than White volunteers (Desta et al., 2002; Dobesh, 2009; Small et al., 2010; Cuisset et al., 2012).

6. Efficacy and safety—Lost in translation?

As previously indicated, disease diagnosis methods in Traditional Chinese Medicine (“Zheng” differentiation) are different to non-Chinese, organ-specific methods. This makes it hard to compare Chinese with Western ‘clinical trial’ results, as very few of the more than 2000 Chinese studies meet the standards of evidence-based medicine (Xu et al., 2012). An extensive review and toxicological evaluation of *Angelica sinensis* (NTP, 2008) concluded that “overall, human studies suggest that there is little evidence to support the use of Dong quai for any condition. Numerous side effects have been reported in clinical studies (e.g., headaches, abnormal heart rhythms, blood pressure abnormalities) and studies suggest that Dong quai may interfere or exacerbate effects produced by numerous drugs and herbs. Acute toxicity studies in animals indicate that administration of Dong quai produced no effects at a dose up to 5000 mg/kg”.

6.1. Efficacy

6.1.1. Premenstrual syndrome and primary dysmenorrhoea

Well controlled trials are lacking with regard to premenstrual syndrome (Jing et al., 2009). For the treatment of primary dysmenorrhoea a TCM formula consisting of *Angelica sinensis*, *Paeonia lactiflora* and *Corydalis yanhusuo* was assessed in The

Netherlands. After the 3rd cycle, 53% of women in the TCM group reported less pain than usual, compared with only 26% in the placebo group (Kennedy et al., 2006). In Taiwan a randomised placebo-controlled trial with Si Wu Tang found a statistically significant reduction in period pain intensity in the first follow-up cycle and suggested a longer treatment phase (Yeh et al., 2007). A very comprehensive Review was carried out by Zhu et al. (2008) into the use of Chinese herbal medicine for primary dysmenorrhoea. Of the 40 trials evaluated mainly carried out in China, 23 used self-designed formulae with *Angelica sinensis* as an ingredient. No single (AS) substance trial was identified. Some trials were deemed too short and many of the included studies were considered to be of low quality. However in general the Review found “promising evidence for the use of Chinese herbal therapy in reducing menstrual pain, with up to three months of effectiveness and with no significant adverse effects being identified” (Zhu et al., 2008).

6.1.2. Menopausal symptoms

Although there is no specific name corresponding to menopausal symptoms in ancient books of TCM, scientists are increasingly evaluating the potential of Chinese herbal medicines and their integration into western systems of medicine (Kwee et al., 2007; Scheid et al., 2010). Using the modified Kupperman Index Delaplaine et al. (1952), Zhou et al. (2007) evaluated the effectiveness of an herbal formula, including *Angelica sinensis*, on the menopausal symptoms in ovariectomised Chinese women. Significant improvements in symptoms were recorded. A critical review into the efficacy and side effects of Chinese herbal medicine for menopausal symptoms also found a degree of efficacy for some menopausal symptoms and few side effects. However none investigated long-term side effects and only two studies out of 23 included *Angelica sinensis* (Xu et al., 2012). An analysis of herbal products used in Taiwan for the alleviation of menopausal symptoms showed that although effective, only a small number contained *Angelica sinensis* and only in combination with *Ligusticum chuanxiang* (Chen et al., 2011).

Ethnic differences in menopausal symptoms and hormone levels have been reported, for example between Chinese and German women (Rampp et al., 2008). Only one well-designed trial using danggui as a single constituent in women of Caucasian origin could be found. An aqueous extract of *Angelica sinensis* (Dong quai standardized to 0.5 mg/kg of ferulic acid) was tested (dose equivalent to 4.5 g root daily) in Californian women. At no stage up to 24 weeks were there any significant differences between the placebo and dong quai regarding menopausal symptoms (hot flushes), endometrial thickness, etc. Used alone it did not produce oestrogen-like responses (Hirata et al., 1997).

In TCM *Angelica sinensis* is normally used in combination with other plants and not as a single ingredient. When postmenopausal Chinese women were given Dang Gui Buxue Tang (*Angelica sinensis* and *Astragalus membranaceus*; 1:5 ratio) the frequency of menopausal mild hot flushes (but not moderate or severe) was reduced (Haines et al., 2008). Another combination product of *Angelica sinensis* and *Matricaria chamomilla* when evaluated in Israeli women decreased the number and intensity of hot flushes (Kupfersztain et al., 2003).

6.2. Safety

6.2.1. Patients taking anti-clotting medications

Dong quai (danggui) is “generally recognized as safe (GRAS)” by the FDA but a number of side effects have been reported (NTP, 2008). Also evidence suggests that patients when taking Chinese herbal medicines are potentially at risk when taking conventional

anti-clotting medications for cardiovascular diseases (Tsai et al., 2013; Williamson et al., 2013). In vitro tests have shown that platelet aggregation was inhibited by an ethanolic (70%) extract of *Angelica sinensis* (Gou et al., 2003) as well as by ferulic acid and coniferyl ferulate (Yu et al., 2009). Z-ligustilide extracted from *Radix Angelicae Sinensis* also decreased platelet aggregation induced by ADP ex vivo and arterio-venous shunt thrombosis in vivo in rats. Ligustilide may exert efficient antithrombotic activity through inhibition of platelet aggregation, without affecting coagulation time of peripheral blood (Zhang et al., 2009b). Studies in rats with danggui (assayed on ferulic acid content) showed antithrombotic effects against venous thrombosis and pulmonary embolism, without potentiating the antithrombotic effect of clopidogrel, but significantly prolonging prothombin time when given in conjunction with clopidogrel (i.e. enhanced bleeding time) (Li and Wang, 2010). The only published human adverse cardiac reaction is of a 46-year-old African-American woman with atrial fibrillation stabilized on warfarin, who experienced a greater than 2-fold elevation in prothombin time and international normalized ratio after taking dong quai concurrently for 4 weeks (Page and Lawrence, 1999).

6.2.2. Women with breast cancer and men with prostate cancer

Potentially both women and men are at risk. A standardized ethanolic extract of *Angelica sinensis* has shown oestrogenic activity in rats (Circosta et al., 2006) and phenolic plant acids (including ferulic acid) increased serum oestradiol (Zych et al., 2009). Weak oestrogen agonistic activity was shown by an aqueous extract of Dong quai and could present a risk for women with oestrogen-sensitive and insensitive breast cancer (Lau et al., 2005). Men with prostate cancer on androgen deprivation therapy sometimes experience hot flashes. A randomized double-blind placebo-controlled trial was carried out with men taking Dong quai for 3 months. No significant differences in the severity, frequency or duration of hot flashes were found in comparison to control (Al-Bareeq et al., 2010).

6.2.3. Patients on drugs that are CYP2D6 and CYP3A4 substrates

The enzyme CYP3A4 facilitates the metabolism of almost 50% of all prescriptions medications, making it one of the most important drug metabolizing enzymes in humans. Of similar importance is CYP2D6 which dictates the pharmacokinetic profiles of many antidepressants, antipsychotics, beta-receptor antagonists, analgesics and anti-arrhythmic agents. Water and ethanol extracts of *Angelica sinensis* increase rat liver CYP2D6 and CYP3A4 activities (Tang et al., 2006), all indicating potential adverse herb-drug interactions with clinical consequences (Zhou et al., 2003; Gurley et al., 2008; Wu et al., 2012).

7. Conclusion

The problems associated with *Angelica sinensis* root are common to many other herbal drugs used in traditional systems of medicine. Translation from one culture to another is fraught with problems, such as language, tradition and method of use, environmental factors, genetics, diet and life-style of users. Danggui is a TCM of long-standing in China with a large amount of historical and modern scientific information associated with it. Many recent research publications using standardised *Angelica sinensis* extracts with identified active constituents do indicate significant haematopoietic, spasmolytic, analgesic, antioxidant, anti-inflammatory, immunomodulatory and anticancer effects, suggesting that the traditional uses are not without scientific basis. However from a clinical viewpoint very few of the many Chinese clinical studies meet the Western standards of evidence-based medicine. Also the

manifestations of many diseases are associated with environmental and genetic factors.

In 1998 the EMEA published a Guidance Note (CPMP/ICH/289/95) on "Ethnic Factors for the Acceptability of Foreign Clinical Data" based on the ICH Harmonised Tripartite Guideline "Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use". This guidance describes how the development of a medicine for a new region can deal with the possibility that ethnic factors could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. "For global development, studies should include populations representative of the regions where the medicine is to be registered and should be conducted according to ICH guidelines". It can be argued that until sufficient, well-controlled clinical trials are carried out with women of Caucasian / European ancestry, using standardized *Angelica sinensis* root/preparations, at a specified dose, for a sufficient period of time, any potential benefits of danggui, as a medicine, remain lost to European women.

Q2 Uncited references

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