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Research paper

The cardiovascular side effects of Ma Huang due to its use in isolation in the Western world

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ABSTRACT

Introduction: An impediment for the acceptance of Traditional Chinese Medicine (TCM) in the West is that the improper use of some TCM is associated with serious side effects. This is exemplified by Ma Huang Decoction (MHD), a Ma Huang containing TCM formula used to treat asthma. The reported cardiovascular side effects often involve the inappropriate use of Ma Huang in isolation, while in TCM clinical practice Ma Huang is combined with other herbs in MHD to mitigate side effects. The aim of the study was to investigate the potential of Ma Huang as it is used in TCM, explore how it may affect the cardiovascular system and compare this to Ma Huang as it is used in the West.

Methods: The contractile response of isolated arteries from human placenta to Ma Huang, MHD, and MHD without Ma Huang was used in a bioassay to evaluate their cardiovascular side effects.

Results: The contractile response by Ma Huang in isolation is much higher than that of Ma Huang in combination with the other herbs in MHD. This confirms that the interplay of the various compounds in MHD may mitigate the side effects of Ma Huang. Previous studies showed that the other herbs in MHD also increase the therapeutic efficacy of Ma Huang. This indicates that the incorrect use of Ma Huang in isolation, and without the supervision of knowledgeable professionals, is likely to be the reasons why the cardiovascular side effects are reported in the West.

Conclusion: To fully value and appreciate its benefit, TCM should be used appropriately as developed over centuries in China.

1. Introduction

Traditional Chinese Medicine (TCM) is the quintessence of the Chinese cultural heritage and has contributed to the Chinese Nation's wealth and prosperity over the past thousands of years. TCM has become an important and fundamental part of the Chinese health care system [1]. It is increasingly realized that TCM is also valuable for the treatment of diseases in Western societies, especially when Western drugs that have been developed fail to be effective [2]. However, to fully appreciate TCM in the West, fundamental differences between the eastern and Western culture need to be understood.

A Western drug is designed to act selectively on a single target. The paradigm in Western medicine is that it is best to isolate active ingredients from *e.g.* herbs, and use the compound that is most active on one specific target [3]. In contrast, the guiding principle in TCM is that herb mixtures should be used. In the mixture, the herbs affect and balance each other to form a strong medical union to treat disease [4,5].

The combination principle of TCM is based on the rule of *"Jun-Chen-Zuo-Shi"* (Fig. 1) [6]. Each herbal ingredient has a specific function, and their interplay makes the therapy more powerful and specific. The "Jun" herb is the principle active herb, having the main effect in treating the disease. The "Chen" herb strengthens the curative effect of the Jun herb. The "Zuo" herb modulates the effects of Jun and Chen and the "Shi" herb harmonizes the effect of the other ingredients. This unison and synergy can be exemplified with the well-known herb formula, Ma Huang Decoction (MHD) used to treat asthma. MHD consists of the following individual herbs in a fixed weight ratio, Ma Huang (*Herba Ephedra, Ephedra Sinica Stapf*): Gui Zhi *(Ramulus Cinnamomi, Cinnamomum cassia Presl*): Xing Ren (*Semen Armeniacae Amarum, Prunus armeniaca* L.): Gan Cao *(Radix Glycyrrhizae, Glycyrrhiza uralensis* Fisch.) = 3:2:2:1 [7,8]. Western studies on TCM focus on the

Abbreviations: TCM, traditional Chinese medicine; MHD, Ma Huang Decoction; FDA, The Food and Drug Administration; KRB, Krebs Ringer bicarbonate buffer

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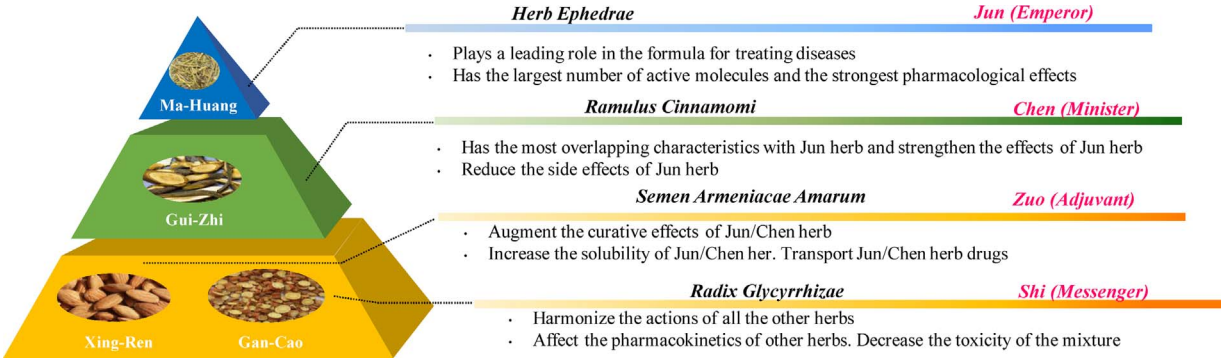

Fig. 1. The diagram representing the combination principle of TCM formula, adapted from Yao et al. [6].

therapeutic effect. However, the main impediment for the introduction of TCM in the Western world is not the lack of evidence on the efficacy, but reports on its toxicity caused by its incorrect use [9–11]. For example, in the United States, Ma Huang has already given rise to serious cardiovascular side effects, like stroke or heart failure [12]. Therefore the United States Food and Drug Administration (FDA) has issued regulation on prohibiting the sale of all supplements containing Ma Huang, and reiterated its advice to stop using these products and also TCM [13], which includes MHD. However, the advice is mainly based on the misuse of Ma Huang, administered in isolation and at a relatively high dose as a slimming agent without the supervision of qualified healthcare professionals [14,15]. This indicates that the advice involves the incorrect use of TCM, and might therefore not be justified. Nonetheless, the advice of the FDA has given TCM a bad reputation. This hampers the introduction of TCM in the West, which is a missed opportunity to profit from the benefits TCM might offer when it is used correctly.

The aim of the study was to examine whether Ma Huang as it is used in TCM is less prone to give cardiovascular side effects compared with the way as it is used in Western Societies. Ephedrine is the most abundant alkaloid in Ma Huang. With a comparable chemical structure to amphetamines, ephedrine works directly or indirectly by stimulating alpha adrenergic receptors, beta adrenergic receptors and trace amine associated receptors [16,17]. This receptor activation by ephedrine has been reported extensively and is probably involved in severe cardiovascular side effects of Ma Huang [18]. We studied the side effects in a bioassay by examining the constriction of human placenta arteries. According to the *"Jun-Chen-Zuo-Shi"* principle, the contractile effect of Ma Huang in MHD should be weakened by the other herbal ingredients in this formula. This would indicate that Ma Huang when used in the traditional manner confines the cardiovascular side effects, and that the total ban by the FDA is an overreaction.

2. Materials and methods

2.1. Chemicals

All chemicals were purchased from Sigma-Aldrich (St, Louis, MO, USA). Krebs Ringer bicarbonate buffer (KRB) contains (in mM): NaCl 118.2, KCl 4.7, $MgSO_4{\cdot}7H_2O$ 1.1, KH_2PO_4 1.2, $NaHCO_3$ 25.0, $CaCl_2$ 2.5, and glucose 5. HEPES buffered salt solution contains (pH 7.4, in mM): NaCl 142.9, KCl 4.7, $MgSO_4{\cdot}7H_2O$ 1.1, KH_2PO_4 1.2, $CaCl_2$ 2.5, glucose 5 and HEPES 15. Water was prepared using a Milli-Q plotwater purification system (Millipore B.V., Amsterdam, the Netherlands).

2.2. Preparation of herb extracts

The raw and dry Chinese herbs were supplied by Chinaturel Import & Export B.V. (Den Haag, the Netherlands). Ma Huang: Gui Zhi: Xing Ren: Gan Cao = 3:2:2:1. Seven mL of 100% distilled water was added to 1 g of MHD. After 30 min at room temperature, the mixture was boiled for 1 h. The extract was centrifuged at 5000 × *g* for 15 min. The supernatant was filtered and stored at −20 °C. Also, an extract of only Ma Huang (the quantity of Ma Huang used was equal to the quantity of Ma Huang in MHD) was prepared according to this procedure as well as an extract of MHD without Ma Huang [19].

2.3. HPLC analysis

The content of ephedrine in Ma Huang and MHD were determined using an Agilent 1260 HPLC system (Agilent Technologies, Inc., USA). The constituents were separated on an Econosphere C18 column (150 × 4.60 mm i.d., 5 µm). The mobile phase consisted of acetonitrile (solvent A) and 0.1% (V/V) trifluoroacetic acid (solvent B) and changed from 0% to 15% A in 10 min, the flow rate of 1.0 mL/min. The sample injection volume was 20 µL. The ultraviolet detection was set at 210 nm. Calibration standards of ephedrine (35–140 µg/mL) were prepared in HPLC grade water. Prior to analysis, the herb extracts were filtered through a 0.2 µm [20]. The concentration of ephedrine in Ma Huang and MHD was calculated based on the peak-height.

2.4. Recording of vasomotor responses

The vasoconstrictive activity was determined *in vitro* on arterial rings obtained from human placentas. The placenta arteries respond very well to various vasoconstrictive agents, including ephedrine and Ma Huang. Moreover, the placenta arteries have a human origin and are obtained from material that is otherwise discarded. The placentas were obtained after full-term pregnancies (> 37 weeks) of nulparria at the Academic Hospital Maastricht and Maastricht University. It is not required to ask the mothers and fathers for their informed consent as the placentas are considered waste material and patients are generally aware this material can be used for scientific experiments as it does not involve a live biological specimen. Placentas were dissected within 1 h after non-pathological delivery. The second and third order branches of chorionic arteries of a fresh placenta were isolated by dissection from surrounding placental tissue in HEPES buffers at room temperature. The artery was then cut into rings approximately 2 mm in length. Isolated arteries segments were stored in HEPES buffer for no longer than 12 h at 4 °C.

The arterial rings were suspended in wire myographs (DMT, Aarhus, Denmark) for the recording of isometric force development. The organ chamber solution (7 mL KRB) was aerated with 95% O_2 and 5% CO_2 and maintained at 37 °C. Each ring was stretched in a stepwise manner to a diameter at which the largest contractile response to 40 mM K^+ was obtained [21]. The optimal lumen diameter of the segments averaged 513 ± 7 µm and contractile responses to 62.5 mM K^+ averaged 1.6 ± 0.2 N/m. Vascular functions were assessed as follows: Arterial rings were stimulated with 62.5 mM K^+ to determine the receptor independent contraction. Then the arterial segments were washed and