Alternative & Integrative Medicine
ISSN: 2327-5162

Liang et al., Altern Integ Med 2013, 2:9
DOI: 10.4172/2327-5162.1000e110

Editorial Open Access

Panax notoginseng: A Double-Edged Sword in Haemostasis?

Willmann Liang*, Ping Chung Leung and David T Yew

Institute of Chinese Medicine, The Chinese University of Hong Kong, Hong Kong, China

Radix Notoginseng (commonly known as notoginseng or san-qi) is an herb primarily indicated for blood- and circulation-related conditions. In traditional Chinese medicine, notoginseng is often used together with other herbs to halt both internal and external bleeding, although the effects are mostly attributed to notoginseng itself [1]. Experimental findings have provided support to other effects, such as anti-inflammatory, anti-fibrotic, immunostimulatory, neuroprotective, of notoginseng as well [2]. The effect on bleeding is, however, more complicated. There is mounting evidence that notoginseng possesses both pro-haemostatic and anti-haemostatic properties. The apparently paradoxical effects may owe to factors including herbal preparation methods, experimental parameters and metabolic activity of the herb. This editorial highlights selected literature which may be of considerable value in future research concerning how notoginseng affects haemostasis.

The normal blood-clotting response after sustaining a tissue injury begins with activation of platelets and the coagulation cascade. Conventional drugs modulate the clotting process either by targeting the platelets, clotting factors or the haemostatic plug itself [3], these being also the postulated sites of action of notoginseng in the experimental studies. Traditionally notoginseng is used to stop bleeding and therefore its pro-haemostatic evidence will be discussed first.

A traditional herbal formulation indicated for external, traumatic injury, Yunnan Bai Yao, of which notoginseng is the most abundant ingredient, has demonstrated comparable hameostatic efficacy as raw notoginseng alone [4]. Bleeding time was significantly shortened when the herbal powder was applied topically [4]. The underlying mechanisms were elucidated to a greater extent in other studies, also with the use of notoginseng constituents. The chemical profile of notoginseng has been studied in detail and major constituents identified [1,5]. Among all constituents, dencichine and the group of saponins are most active in promoting haemostasis. Zhao and Wang showed that intraperitoneal injection of dencichine shortened bleeding time by increasing the platelet number count [6]. No other studies followed up on dencichine, unlike notoginseng total saponins (NTS) which were investigated more extensively. Alcohol was used to extract NTS from raw notoginseng [7,8]. Topical application of both raw notoginseng powder and NTS powder were equally effective in shortening bleeding time [7]. In contrary, the water extract of notoginseng has only weak haemostatic effect [7] and may be attributed to dencichine, which is water-soluble [6]. Further analysis of the haemostatic effect of individual NTS showed that the notoginsenoside Ft1 was among the strongest pro-haemostatic saponin in notoginseng [9]. Similar to dencichine, Ft1 also exerted its action on platelets, activating the ADP ($P2Y_{12}$) receptor to initiate platelet aggregation [9]. Parameters of coagulation, such as prothrombin time, activated partial thromboplastin time and thrombin time, were also lengthened after Ft1 treatment [9]. This study [9] did not examine the haemostatic effect of raw notoginseng (water or alcohol extract) or dencichine, which will be of value to compare the efficacy of the various samples in the same experimental setting. Nevertheless, the enhanced platelet activity of NTS (notably Ft1) has been demonstrated. It remains to be seen though whether other participants of the haemostatic process are also positively modulated by NTS.

Interestingly enough, notoginseng (and NTS) also exhibit anti-haemostatic actions, making the herb potentially dangerous of excessive bleeding when used in combination with antiplatelet and anticoagulant drugs [1]. The methanol extract of notoginseng, yielding mostly NTS, showed antiplatelet and anticoagulant effects [10] in *in vitro* and *in vivo* assays. It is worth noting that this study [10] also demonstrated that steaming the notoginseng extract augmented the anti-haemostatic effects as compared to the raw extract. In Lau et al. [10], notoginseng was fed orally [10], as opposed to topical application (at the site of injury) in the pro-haemostatic studies [7,8]. It is possible that the oral route (after first-pass metabolism) may inactivate the pro-haemostatic constituents of notoginseng while unmasking the effects of the anti-haemostatic ones. On the other hand, dencichine given orally to rats failed to alter bleeding time [10], a result different from the Zhao and Wang study where the drug was injected by the intraperitoneal route [6]. In a study where human blood samples were used, the water extract of notoginseng had only modest anticoagulant effect [11,12], suggesting that the major anti-haemostatic constituents likely remained in the methanol extract. Unlike the pro-haemostatic actions confining to the platelets as demonstrated so far, the anti-haemostatic effects are more diverse in that other cell types as well as both pre- and post-clotting events are affected. For example, coagulation was inhibited in NB4 cells that were used as a model of acute promyelocytic leukemia to examine disseminated intravascular coagulation [12]. In endothelial and smooth muscle cells, the notoginsenoside R1 dissolved the haemostatic plug by stimulating the synthesis of tissue plasminogen activator [13,14].

Collectively, separate studies have demonstrated both pro-haemostatic and anti-haemostatic effects of notoginseng and its constituents. Gao et al. [9] showed that different NTS may either increase or decrease platelet aggregation in the same experimental setting [9], further supporting the apparently contradicting results obtained by others. The source of the herbs aside, however, discrepancy in findings may also arise from different preparation methods (e.g. raw, water extract, ethanol extract, methanol extract, steamed methanol extract), in that different constituents may be preserved (or lost) after the procedures. The route of administration is another crucial determinant of pro- or anti-haemostatic activity, as it seems that topical application [7,8] and oral administration [10] gave opposite results. Recently, the pharmacokinetic aspects of notoginseng after oral administration have been studied by comparing the constituent concentrations in

***Corresponding author:** Willmann Liang, E204 Science Centre East Block, Institute of Chinese Medicine, The Chinese University of Hong Kong, Hong Kong, China, Tel: 852-3943-4370; E-mail: willmann@cuhk.edu.hk

Received November 15, 2013; **Accepted** November 16, 2013; **Published** November 16, 2013

Citation: Liang W, Leung PC, Yew DT (2013) *Panax notoginseng*: A Double-Edged Sword in Haemostasis? Altern Integ Med 2: e110. doi:10.4172/2327-5162.1000e110

plasma, bile and urine [15,16]. It will be of interest to further assess the biological, namely pro-haemostatic and anti-haemostatic, activity of the constituents after having undergone metabolism. With more advanced chromatographic and spectrometric technologies in place, previously unknown constituents of notoginseng are also being identified [5]. Whether these newly discovered constituents possess significant biological effects is yet to be determined. The interplay between constituents in a raw herb may be as important as, if not more than, the effect elicited by individual compounds purified after series of extraction.

References

1. Chen JK, Chen TT (2004) Chinese medical herbology and pharmacology. Art of Medicine Press, Inc., City of Industry, CA.
2. Ng TB (2006) Pharmacological activity of sanchi ginseng (Panax notoginseng). J Pharm Pharmacol 58: 1007-1019.
3. Katzung BG, Masters SB, Trevor AJ (2011) Basic and clinical pharmacology. (11thedn), The McGraw-Hill Companies, Inc, Singapore.
4. Fan C, Song J, White CM (2005) A comparision of the hemostatic effects of notoginseng and yun nan bai yao to placebo control. J Herb Pharmacother 5: 1-5.
5. Yang WZ, Ye M, Qiao X, Liu CF, Miao WJ, et al. (2012) A strategy for efficient discovery of new natural compounds by integrating orthogonal column chromatography and liquid chromatography/mass spectrometry analysis: its application in Panax ginseng, Panax quinquefolium and Panax notoginseng to characterize 437 potential new ginsenosides. Anal Chim Acta 739: 56-66.
6. Zhao G, Wang X (1986) Dencichine-hemostatic constituent of san qi. Zhong Cao Yao 17: 34-35.
7. White CM, Fan C, Chow M (2000) An evaluation of the hemostatic effect of externally applied notoginseng and notoginseng total saponins. J Clin Pharmacol 40: 1150-1153.
8. White CM, Fan C, Song J, Tsikouris JP, Chow M (2001) An evaluation of the hemostatic effects of hydrophilic, alcohol, and lipophilic extracts of notoginseng. Pharmacotherapy 21: 773-777.
9. Gao B, Huang L, Liu H, Wu H, Zhang E, et al. (2013) Platelet P2Y12 receptor involved in the hemostatic effect of notoginsenoside Ft1, a saponin isolated from Panax notoginseng. Br J Pharmacol.
10. Lau AJ, Toh DF, Chua TK, Pang YK, Woo SO, et al. (2009) Antiplatelet and anticoagulant effects of Panax notoginseng: comparison of raw and steamed Panax notoginseng with Panax ginseng and Panax quinquefolium. J Ethnopharmacol 125: 380-386.
11. Li CT, Wang HB, Xu BJ (2013) A comparative study on anticoagulant activities of three Chinese herbal medicines from the genus Panax and anticoagulant activities of ginsenosides Rg1 and Rg2. Pharm Biol 51: 1077-1080.
12. Li XH, Dong ZR, Hao HL (2004) [Effect of panax notoginseng saponin on procoagulant activity and differentiation induction in NB4 cells]. Zhongguo Zhong Xi Yi Jie He Za Zhi 24: 63-66.
13. Zhang W, Wojta J, Binder BR (1994) Effect of notoginsenoside R1 on the synthesis of tissue-type plasminogen activator and plasminogen activator inhibitor-1 in cultured human umbilical vein endothelial cells. Arterioscler Thromb 14: 1040-1046.
14. Zhang WJ, Wojta J, Binder BR (1997) Effect of notoginsenoside R1 on the synthesis of components of the fibrinolytic system in cultured smooth muscle cells of human pulmonary artery. Cell Mol Biol (Noisy-le-grand) 43: 581-587.
15. Wen XD, Yang J, Ma RH, Gao W, Qi LW, et al. (2012) Analysis of Panax notoginseng metabolites in rat bile by liquid chromatography-quadrupole time-of-flight mass spectrometry with microdialysis sampling. J Chromatogr B Analyt Technol Biomed Life Sci 895-896: 162-8.
16. Hu Z, Yang J, Cheng C, Huang Y Du F, et al. (2013) Combinatorial metabolism notably affects human systemic exposure to ginsenosides from orally administered extract of Panax notoginseng roots (sanqi). Drug Metab Dispos 41: 1457-1469.