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Danqi Piantan Jiaonang Does Not Modify Hemostasis, Hematology, and Biochemistry in Normal Subjects and Stroke Patients

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Key Words
Danqi Piantan Jiaonang, stroke · Traditional Chinese medicine · Safety studies

Abstract
Background and Objective: Previous studies on Danqi Piantan Jiaonang (DPJ, NeuroAid®), a traditional Chinese medicine, in stroke patients showed promising results. Our aim was to determine the safety of DPJ in normal subjects and stroke patients through a series of studies assessing its immediate and long-term effects, alone and in combination with aspirin, on hematological, hemostatic, and biochemical parameters. ***Methods:*** We conducted 3 studies from December 2004 to May 2006. Study 1 was a case series which recruited 32 healthy volunteers who were given 2 oral doses of 4 DPJ capsules (0.4 g/capsule) 6 h apart. Study 2 was a randomized controlled trial of 22 healthy volunteers who received either 1 oral dose of aspirin 300 mg alone or a combination of 1 dose of aspirin 300 mg and 2 doses of 4 DPJ capsules taken 6 h apart. For both studies 1 and 2, hemostatic parameters (prothrombin time, activated partial thromboplastin time, fibrinogen, platelet aggregation, D-dimer) were tested at baseline, and after 2 and 8 h. Study 3 was a case series which recruited 10 patients with recent ischemic stroke (within 7 days) who were given 4 DPJ capsules taken orally 3 times a day for 1 month. Blood tests for hemostatic, hematological (complete blood count), and biochemical parameters (glucose, creatinine, alanine aminotransferase, aspartate transaminase, C-reactive protein) were performed at baseline, and after 1 and 4 weeks. ***Results:*** Apart from the expected changes in platelet aggregation in subjects taking aspirin, no significant differences were detected in hemostatic parameters at baseline, and 2 and 8 h after oral intake of DPJ alone or in combination with aspirin. Likewise, no significant differences were observed in hematological, hemostatic, and biochemical parameters at baseline, and after 1 and 4 weeks of oral intake of DPJ. ***Conclusion:*** DPJ does not significantly modify hematological, hemostatic, and biochemical parameters in normal subjects and stroke patients.

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Stroke is the third leading cause of death worldwide and a major cause of morbidity [1]. Although prevention is the most effective way to decrease the burden of stroke [2], acute stroke treatment aims at reducing mortality and disability. So far, only 3 therapeutic measures have demonstrated efficacy in reducing disability and/or mortality in randomized clinical trials, namely intravenous recombinant tissue plasminogen activator [3], which can be used in only <5% of patients with ischemic stroke, aspirin [4], which is less effective but applicable to most ischemic stroke patients, and stroke unit care [5], which can be of benefit to all stroke patients.

While neuroprotective substances have overwhelmingly shown promise in laboratory studies, none has been found to be beneficial in clinical trials [6]. Traditional Chinese medicines (TCM), therefore, provide an attractive opportunity for exploration. Over 100 TCM products are currently used clinically for stroke in China with the approval of the Chinese National Drug Administration. Danqi Piantan Jiaonang (DPJ) is registered with the Sino-FDA for 'stroke recovery' on the basis of the results of clinical studies that included more than 600 stroke patients between 2 weeks and 6 months of stroke onset [unpubl. data].

Before embarking on an acute ischemic stroke clinical trial performed according to international standards, we assessed the immediate and long-term effects of DPJ, alone and in combination with aspirin, through a series of studies on various hemostatic, hematological, and biochemical parameters among normal subjects and stroke patients.

Methods

A series of 3 related studies were conducted from December 2004 to May 2006 in the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine.

Subjects

Normal healthy volunteers were recruited who were between 21 and 65 years old, were willing to be on a fat-restricted diet during the study, had no history of easy bruising or blood coagulation disorder, and had not taken aspirin, anticoagulants, antiplatelet medication, any investigational drug, or TCM within 1 month prior to participation. Since these were early-phase studies, age was capped at 65 years to avoid inclusion of older subjects with unrecognized underlying medical conditions that may put them at higher risk of complications from study procedures and medications. Women should not be pregnant, lactating or nursing. Intake of TCM other than the study drug was not allowed during the study.

Patients with ischemic stroke were recruited who were 18 years old or older, presented within the first week of stroke onset, had a computed tomography scan or magnetic resonance imaging compatible with cerebral infarction and no evidence of intracranial hemorrhage, had no history of easy bruising or blood coagulation disorder, had not received thrombolysis, and had not taken TCM or any investigational drug within 3 months prior to participation. Women should not be pregnant, lactating or nursing.

Study Drug

DPJ or NeuroAid® administered in all 3 studies was supplied, packaged and distributed by Tianjin Shitian Pharmaceutical Industry Co., Ltd. and labeled according to the requirements of local laws and regulations. It has been registered with the Sino-FDA since August 2001 for the treatment of stroke recovery, is approved as a Chinese proprietary medicine in Singapore, and approved for distribution by the Bureau of Food and Drugs in the Philippines. Each capsule combines 10 herbal components [i.e. root of membranous milk vetch, red sage root, red peony root, rhizome of *Ligusticum chuanxiong,* root and rhizome of *Panax notoginseng,* bark of subshrubby peony (cortex moutan), wood of odoriferous rosewood, *Uncaria gambir* plant stem with hooks, root of thinleaf milkwort, rhizome of grassleaf sweetflag] and 4 animal components (i.e. *Hirudo nipponica* Whitman, *Eupolyphaga* or *Steleophaga, Buthus martensii* Karsch, calculus bovis artifactus). The dose of DPJ as approved by the Sino-FDA is 4 capsules 3 times a day and is the dose used in these studies.

Aspirin was supplied by Tianjin Hospital or by Tianjin Shitian Pharmaceutical Industry Co., Ltd.

Laboratory Procedures

Subjects were asked to remain comfortably seated or lying down for at least 30 min before each blood sample was collected by venipuncture. All clinical laboratory evaluations were conducted under the supervision of Prof. Jiao Lianting and in accordance with the standards of the Biology Laboratory at the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine.

Testing of hemostatic parameters included the Quick prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, platelet aggregation, and D-dimer. Platelet aggregation studies were performed by the turbidimetric method (LBY NJ4 platelet aggregometer, PRECIL, Beijing Pu-Ii-sheng Corporation) using 16.5 μmol/l ADP as agonist (concentration 300 μmol/l; 11 μl added in 200 μl specimen). Testing of hematological and biochemical parameters included complete blood count, creatinine, alanine aminotransferase, aspartate transaminase, fasting glucose, and C-reactive protein.

Study 1

Healthy volunteers (n = 32) received 2 oral doses of 4 DPJ capsules (0.4 g/capsule) taken 6 h apart. Blood samples for testing of hemostatic parameters were taken at baseline (before intake of the first dose of DPJ), 2 h after the first dose of DPJ, and 8 h after the first dose of DPJ (or 2 h after the second dose of DPJ).

Study 2

Healthy volunteers (n = 22) were randomized to receive either 1 oral dose of aspirin 300 mg alone or a combination of 1 oral dose of aspirin 300 mg and 2 oral doses of 4 DPJ capsules (0.4 g/capsule)

taken 6 h apart. A dose of 300 mg of aspirin was selected to reduce the chance of failing to detect an interaction with DPJ and because some medical practitioners in other countries prescribe this dose. Treatment allocations were prerandomized and assigned to the subjects in the sequence in which they arrived at the center. Blood samples for testing of hemostatic parameters were taken at baseline (before intake of the first dose of DPJ), 2 h after the first dose of DPJ, and 8 h after the first dose of DPJ (or 2 h after the second dose of DPJ). Subjects were not blinded to the assigned treatment but the laboratory personnel performing the tests were not aware of treatment allocations.

Study 3

Patients with ischemic stroke (n = 10) received 4 DPJ capsules (0.4 g/capsule) taken orally 3 times a day for 1 month. Intake of aspirin and other standard medications for associated medical conditions, such as diabetes mellitus, hypertension, hypercholesterolemia, and ischemic heart disease, was allowed. Other traditional Chinese medications were not allowed. Blood samples for testing of hemostatic, hematological, and biochemical parameters were taken at baseline (before intake of the first dose of DPJ), and 1 and 4 weeks after initiation of DPJ.

Adverse events were monitored for and recorded in all 3 studies. Adverse event was defined as any untoward, unfavorable, or unintended medical occurrence, signs, symptoms, or disease observed during the course of each study that may or may not necessarily have a causal relationship with the treatment being investigated.

Ethical Considerations

All 3 study protocols were approved by the Institutional Review Board of the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine. Informed consent was obtained from all participants and the studies were conducted in accordance with the Declaration of Helsinki (October 2000), the applicable guidelines for good clinical practice (ICH-GCP), or the applicable laws and regulations of China.

Statistical Analyses

Descriptive analyses were expressed as means, standard deviations, and/or ranges. The means of continuous outcomes between groups were compared using the t test/paired t test and ANOVA/repeated-measures ANOVA were used and 95% confidence interval (CI) estimates calculated for the difference in means. To specifically test the hypothesis that DPJ does not worsen the coagulation parameters by a clinically significant amount, we a priori defined the following thresholds: PT not to be extended by more than 1 s, aPTT not to be extended by more than 2 s, fibrinogen not to be decreased by more than 0.2 g/l, platelet aggregation not to be decreased by more than 10%, and D-dimer not to be decreased by more than 0.5 mg/l. Thus if the upper limits of the 95% CI of the mean difference were less than 1 s for PT and 2 s for aPTT, this would be strong evidence that DPJ did not clinically significantly prolong the clotting times. Likewise if the lower limits of the 95% CI of the mean difference were greater than –0.2 g/l for fibrinogen, –10% for platelet aggregation and –0.5 mg/l for D-dimer, this would be strong evidence that DPJ did not clinically significantly decrease the value of these coagulation parameters.

Results

Study 1

Among the 32 subjects (13 women and 19 men; mean age 35 years, range 21–65 years), 1 (subject 14) was withdrawn due to abnormal baseline blood test results. Among the remaining 31 subjects, no significant differences were observed in the hemostatic parameters tested 2 h after the first dose of DPJ and 8 h after intake of DPJ (or 2 h after the second dose of DPJ) compared to baseline (table 1). No adverse events were observed.

Study 2

Among the 22 subjects (12 women and 10 men), 11 received aspirin alone (mean age 37 years, range 24–55 years) while the other 11 received aspirin + DPJ (mean age 31 years, range 24–49 years).

As expected, mean platelet aggregation was gradually reduced over time since both groups received aspirin. However, no significant differences were observed in the other hemostatic parameters tested 2 and 8 h after the first dose of DPJ (or 2 h after the second dose of DPJ) compared to baseline, and between the aspirin and aspirin + DPJ groups in all laboratory parameters at every time point (table 2). No adverse events were observed.

Study 3

Ten patients (6 women and 4 men; mean age 65 years, range 45–85 years) were recruited at an average of 3 days after ischemic stroke onset. One woman (patient 6) suffered a recurrent stroke within the first week of the study and did not complete the protocol.

Concomitant medications taken by patients included aspirin in 6 patients, nitrate in 6, antihypertensive medication in 7, oral hypoglycemic agent in 2, fibrate in 1, anticonvulsant in 1, and potassium supplement in 1.

Mean platelet aggregation was reduced over time as expected in patients receiving aspirin. No significant differences were observed in hemostatic, hematological, and biochemical parameters tested 1 and 4 weeks after initiation of DPJ compared to baseline (tables 3, 4). No other adverse events were observed.

Discussion

In our series of safety studies, we showed that intake of DPJ does not affect hemostasis, hematological, and biochemical parameters in normal subjects and stroke patients. These results will be reassuring and helpful

Table 1. Study 1 hemostatic blood test results at baseline, 2 h after the first dose, and 8 h after the first dose (2 h after the second dose) of DPJ

Tests	Baseline results	At 2 h			At 8 h		
		results	mean change	clinically worse	results	mean change	clinically worse
PT, s	12.8 ± 0.7 (11.2 – 14.1)	12.7 ± 0.7 (11.2 – 14.0)	–0.05 (–0.19 to 0.10)	no	12.9 ± 0.7 (11.6 – 14.5)	0.16 (0.02–0.31)	no
aPTT, s	37.6 ± 4.3 (31.2 – 46.9)	37.2 ± 4.4 (30.2 – 46.6)	–0.49 (–1.09 to 0.10)	no	38.7 ± 4.3 (32.2 – 47.2)	1.02 (0.40–1.65)	no
Fibrinogen, g/l	2.98 ± 0.61 (1.79 – 4.22)	3.05 ± 0.59 (1.92 – 4.19)	0.07 (–0.02 to 0.16)	no	3.06 ± 0.57 (2.11 – 4.19)	0.08 (–0.03 to 0.20)	no
Platelet aggregation, %	63.0 ± 15.5 (29.8 – 85.0)	62.2 ± 12.1 (39.1 – 79.2)	–0.82 (–6.9 to 5.2)	no	61.5 ± 13.4 (37.4 – 84.7)	–1.5 (–8.5 to 5.48)	no
D-dimer, mg/l	0.05 ± 0.05 (0 – 0.1)	0.15 ± 0.44 (0 – 2.5)	0.10 (–0.05 to 0.26)	no	0.07 ± 0.05 (0 – 0.2)	0.02 (0–0.05)	no

Values presented are means ± SD, with ranges in parentheses (n = 31). Mean changes at 2 and 8 h are from baseline with 95% CIs. The assessment of nonclinically significant changes at both time points was based on the following thresholds: PT not extended by more than 1 s, aPTT not extended by more than 2 s, fibrinogen not decreased by more than 0.2 g/l, platelet aggregation not decreased by more than 10%, D-dimer not decreased by more than 0.5 mg/l.

when designing future randomized clinical trials on the role of DPJ in acute stroke and stroke recovery.

Intravenous thrombolytic for acute ischemic stroke can be given to only less than 5% of stroke patients because of the short therapeutic time window of 3 h and the increased risk of bleeding [7]. Aspirin, on the other hand, can be given within 48 h of onset to many more patients with acute ischemic stroke but has much less efficacy [4]. These limitations in the utility of established treatments for acute stroke often lead to calls for an intensive search for other modes of intervention to improve stroke recovery and reduce mortality. The concept of neuroprotection as a therapeutic strategy has been of much interest to researchers in the recent years. However, despite thousands of substances that have shown promise in the laboratory, not a single one of more than a hundred clinical trials was able to confirm a beneficial effect [6], making the search for other effective acute stroke treatments even more urgent.

Because of the wide use and experience in China, TCM have the potential to fill this gap in stroke treatment. However, the use of TCM is particularly challenging for clinicians trained in 'western medicine' because of unfamiliarity with the treatment principles in traditional medicine and the lack of adequate evidence from safety and efficacy studies of good standard deemed acceptable to mainstream practitioners.

Wu et al. [8] systematically reviewed 59 traditional Chinese patent medicines for ischemic stroke, of which only 22 have clinical trials eligible for review. The trials were mostly of poor methodological quality, but 8 drugs (milk vetch, Mailuoning, *Ginkgo biloba,* ligustrazine, danshen agents, xuesetong, puerarin, and *Acanthopanax*) were recommended as further research priorities. The TCM drugs chosen for further clinical development, however, must first be tested for efficacy and safety in preclinical and early clinical phase research [9].

DPJ is an agent that contains milk vetch (huangqi) and red sage root (danshen). It is widely prescribed to stroke patients in China. Information on how DPJ was initially developed and the exact rationale behind the inclusion of extracts and components from 10 herbal sources and 4 animals is unclear. However, danshen is among the most popular medicinal herbs used in China to which huangqi has eventually been added in some preparations to improve its purported efficacy [10]. A few unpublished earlier animal studies on DPJ conducted in China and made available to the authors hinted at a possible neuroprotective mechanism when enteral administration of high doses of DPJ in rats and gerbils 2 h before middle cerebral artery occlusion resulted in a smaller infarct size and significant improvement in behavioral disorder from stroke.

Table 2. Study 2 hemostatic blood test results at baseline, 2 h, and 8 h by treatment group

Tests		Aspirin group (n = 11)	Aspirin + DPJ group (n = 11)	p value
PT, s	baseline	12.9 ± 0.3 (12.4–13.4)	12.7 ± 0.4 (12.2–13.7)	0.14
	2 h	12.6 ± 0.4 (11.8–13.3)	12.6 ± 0.4 (11.9–13.3)	0.64
	mean change	–0.26 (–0.44 to –0.09)	–0.05 (–0.22 to 0.13)	0.08
	8 h	12.4 ± 0.4 (12.0–13.3)	12.4 ± 0.5 (11.6–13.4)	0.82
	mean change	–0.47 (–0.75 to –0.20)	–0.27 (–0.53 to –0.02)	0.24
aPTT, s	baseline	38.8 ± 3.4 (32.9–47.2)	37.1 ± 4.0 (30.7–44.1)	0.18
	2 h	39.0 ± 2.6 (33.3–42.4)	38.2 ± 3.5 (32.7–44.6)	0.36
	mean change	0.19 (–1.16 to 1.54)	1.06 (–0.20 to 2.32)	0.15
	8 h	38.2 ± 3.7 (31.0–46.7)	37.2 ± 3.8 (32.5–45.2)	0.22
	mean change	–0.60 (–1.43 to 0.23)	0.04 (–0.89 to –0.96)	0.17
Fibrinogen, g/l	baseline	3.17 ± 0.70 (2.15–4.82)	3.20 ± 0.59 (2.04–4.07)	0.65
	2 h	3.17 ± 0.77 (2.29–5.04)	3.04 ± 0.66 (1.86–3.94)	0.92
	mean change	0 (–1.13 to 0.11)	–0.17 (–0.30 to –0.03)	0.13
	8 h	2.99 ± 0.66 (2.00–4.49)	2.95 ± 0.62 (1.87–3.99)	0.92
	mean change	–0.18 (–0.35 to –0.02)	–0.25 (–0.41 to –0.09)	0.74
Platelet aggregation, %	baseline	62.8 ± 10.0 (51.2–81.3)	61.8 ± 9.8 (46.6–73.3)	0.77
	2 h	62.9 ± 9.0 (49.2–82.6)	58.3 ± 11.2 (39.0–75.6)	0.31
	mean change	0.06 (–8.77 to 8.88)	–3.55 (–12.91 to 5.82)	0.61
	8 h	48.0 ± 15.4 (13.4–69.4)	47.0 ± 5.6 (35.6–54.4)	0.49
	mean change	–14.81 (–26.44 to –3.17)	–14.85 (–21.49 to –8.21)	0.75
D-dimer, mg/l	baseline	0.16 ± 0.13 (0.02–0.46)	0.13 ± 0.06 (0.04–0.23)	0.95
	2 h	0.16 ± 0.13 (0.03–0.43)	0.09 ± 0.07 (0.02–0.24)	0.27
	mean change	0 (–0.03 to 0.03)	–0.04 (–0.07 to 0.00)	0.08
	8 h	0.16 ± 0.13 (0.01–0.41)	0.15 ± 0.13 (0.05–0.48)	0.90
	mean change	0 (–0.03 to –0.04)	–0.02 (–0.04 to 0.08)	1.00

Values presented are means ± SD, with ranges in parentheses. Mean changes at 2 and 8 h are from baseline with 95% CIs. p values were derived using the Mann-Whitney U test comparing means and mean changes between the aspirin group and aspirin + DPJ group at each time point.

Toxicity studies on rats fed up to 18 g/kg/day of DPJ for 3 months showed no effects on hematology, biochemistry (hepatic and renal), and histopathology. Acute toxicity studies on mice (given 80 g/kg DPJ) and rats (given 30 g/kg DPJ) resulted in no death within 7 days and only transient reduction in animal activity. An LD_{50} study conducted at the Department of Science and Technology (Philippines) showed no deaths in mice even after administration of 45 g/kg of DPJ, above which the maximum limit a mouse can normally take would be exceeded and results would be inaccurate since death may occur due to bloating. Toxidrome observed included increased motor activity, defecation, and grooming followed by decreased motor activity and respiratory rate, urination, and excretion of sample. No other adverse/abnormal signs or death occurred within the 14 days of observation.

Currently, an estimated half a million stroke patients, mostly in China, have received DPJ with reportedly promising outcomes and excellent tolerance [unpubl. data]. We, therefore, reckon that DPJ may be a valuable agent to assess for safety, and eventually test for efficacy in a well-designed randomized trial.

Most currently available stroke treatments in the market are for secondary prevention of recurrent vascular events. Antiplatelet agents reduce the risk of a myocardial infarction, stroke, or vascular death by about 23% [11]. Aspirin by far is the most widely used because of its low cost and significant benefit from a public health point of view.

Table 3. Study 3 hemostatic blood test results at baseline, after 1 week of treatment, and after 1 month of treatment with DPJ

Laboratory test	Baseline results	At 1 week			At 1 month		
		results	mean change	clinically worse	results	mean change	clinically worse
PT, s	13.0 (11.6–14.3)	12.5 (11.1–14.4)	–0.54 (–1.08 to –0.01)	no	12.4 (11.5–13.7)	–0.63 (–1.16 to –0.11)	no
aPTT, s	31.0 (27.1–33.5)	32.1 (28.6–38.2)	1.14 (–1.23 to 3.52)	n.s.	30.7 (28.5–34.7)	–0.28 (–2.49 to 1.93)	no
Fibrinogen, g/l	4.10 (2.52–5.77)	4.03 (3.01–6.76)	–0.07 (–1.14 to 0.99)	n.s.	4.06 (3.11–6.71)	–0.04 (–1.31 to 1.23)	n.s.
Platelet aggregation, %	63.6 (51.2–77.2)	52.3 (37.5–70.2)	–11.30 (–22.62 to 0.02)	n.s.	48.4 (33.1–71.9)	–15.16 (–29.88 to –0.45)	n.s.
D-dimer, mg/l	0.25 (0.08–0.65)	0.45 (0.10–1.80)	0.20 (–0.17 to 0.58)	no	0.49 (0.10–2.38)	0.24 (–0.28 to 0.77)	no

Values presented are means with ranges in parentheses (n = 9). Mean changes at 1 week and 1 month are from baseline with 95% CIs. The assessment of nonclinically significant changes at both time points was based on the same thresholds as used in table 1.

Table 4. Study 3 hematological and biochemical blood test results at baseline, after 1 week of treatment, and after 1 month of treatment with DPJ

Laboratory test	Normal values	Baseline	At 1 week	At 1 month
Red blood cells ($\times 10^{12}$)	4.2–5.9	4.42 (3.48–5.14)	4.51 (3.73–5.31)	4.56 (3.70–5.36)
Mean red blood cell volume, fl	86–98	90.7 (83.6–99.2)	90.9 (83.3–97.9)	90.1 (83.2–100.0)
White blood cells ($\times 10^{9}$)	4.3–10.8	6.6 (3.7–9.4)	5.9 (3.7–9.4)	6.7 (3.5–12.8)
Hemoglobin, g/l	120–180	139.6 (109–163)	142.9 (120–167)	143.7 (116–162)
Hematocrit, %	37–48 (female) 45–52 (male)	40.0 (31.0–46.1)	41.7 (33.5–47.3)	41.0 (33.5–45.0)
Platelets count ($\times 10^{3}$)	150–450	186.0 (135–246)	214.9 (174-271)	196.4 (135–250)
Creatinine, μmol/l	70–150	70.6 (43–100)	75.6 (51–105)	67.9 (44–89)
SGPT-ALT, IU/l	4–46	13.9 (8.9–20.3)	20.8 (8.1–38.7)	17.8 (9.7–33.4)
SGOT-AST, IU/l	5–40	19.1 (12.4–44.0)	18.1 (11.1–32.0)	16.1 (11.3–23.4)
Glucose, mmol/l	4–6	5.88 (3.93–10.14)	5.21 (3.59–8.49)	4.91 (3.53–6.83)
C-reactive protein, mg/dl	<1	2.04 (0.14–6.42)	1.90 (0.10–11.10)	1.06 (0.10–5.44)

Values presented are means with ranges in parentheses (n = 9).

To test if DPJ has any effect on clotting and coagulation in humans to explain its reported apparent benefit in stroke and being cognizant of the fact that ischemic strokes have a risk of hemorrhagic conversion, we tested oral DPJ for its effect on hemostatic parameters and found no such effect in our subjects. Furthermore, as DPJ would be given as an add-on treatment if proven beneficial, we tested it in combination with aspirin and confirmed that it does not potentiate the effect of aspirin on hemostatic parameters and thereby may not increase the risk of bleeding beyond that attributable to aspirin. We also found that long-term multiple-dose intake of DPJ, which is how it is prescribed in China, does not cause hematological or biochemical adverse effects in our study patients.

While many of the TCM for stroke are allegedly effective because they improve blood circulation and reduce stasis, our findings suggest that DPJ may work by mecha-

nisms other than by its mere effect on platelets and coagulation. If indeed DPJ is effective in improving stroke recovery, it may be reasonable to likewise investigate its role in neuronal protection and plasticity.

The small sample size and inclusion of only subjects of Asian origin are the main limitations to these preliminary safety studies on DPJ. A future large multicenter study will help address these limitations. Nonetheless, in these studies conducted on normal subjects and stroke patients, albeit small, we have demonstrated that short- and long-term intake of DPJ (NeuroAid®) does not significantly modify hemostasis, hematological, and biochemical parameters.

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Erratum

The authors of the article 'Danqi Piantan Jiaonang Does Not Modify Hemostasis, Hematology, and Biochemistry in Normal Subjects and Stroke Patients' (Cerebrovasc Dis 2008;25:450–456) received a notification from the manufacturer regarding an error in the declaration of the ingredients of the study drug. The components of the study drug listed under the section 'Study Drug' on p. 451, third sentence, should read: Each capsule combines 9 herbal components [i.e. root of membranous milk vetch, red sage root, red peony root, rhizome of *Ligusticum chuanxiong,* root of thinleaf milkwort, rhizome of grassleaf sweetflag, root of Chinese angelica, safflower, peach seed *(Prunus persica)*] and 5 animal components (i.e. *Whitmania pigra* Whitman, *Eupolyphaga seu Steleophaga, Buthus martensii* Karsch, calculus bovis artifactus, cornu saigae tataricae).