Garlic at Dietary Doses Does Not Impair Platelet Function

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BACKGROUND: *In vitro* studies suggest that various bioactive constituents of *Allium sativum* (garlic) inhibit platelet function. The extent, however, to which dietary doses of garlic influence platelet function remains unknown. Therefore, we tested the effect of raw garlic on platelet function using point-of-care monitoring devices sensitive for cyclooxygenase I-inhibition and platelet adhesion.

METHODS: Whole blood from 18 healthy volunteers was investigated before and 5 h after ingestion of the study medication consisting of Greek tsatsiki with 4.2 g raw garlic (verum), or Greek tsatsiki without garlic (placebo), in a randomized, crossover, observer-blinded, placebo-controlled study. The potential long-term effects of garlic were investigated in five volunteers after daily ingestion of 4.2 g of raw garlic over 1 wk. Platelet function was assessed with the Platelet Function Analyzer (PFA-100®), impedance aggregometry (Multiplate®), and thrombelastographic Platelet Mapping™. *In vitro* experiments were performed to prove the sensitivity of the assays to garlic-induced platelet inhibition.

RESULTS: Baseline values of platelet function were within normal range in all volunteers. Platelet function was not impaired by single and repeated oral consumption of Greek tsatsiki containing raw garlic in any point-of-care monitoring test used.

CONCLUSIONS: Platelet function is not impaired by single and repeated oral consumption of a dietary dose of garlic in healthy volunteers. Dishes containing socially acceptable doses of raw garlic are unlikely to increase the risk of perioperative bleeding. Further studies are warranted to determine the potential additive effects of platelet-inhibiting drugs combined with garlic and other herbs.

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The use of herbal remedies has become more widespread, driven by the belief that natural substances have fewer side effects than pharmaceuticals, as well as their ready availability to the public without prescriptions or visits to health providers. Garlic (*Allium sativum*) is among the most commonly used medicinal plants in presurgical patients (1,2). Caring for patients perioperatively taking mostly self-administered herbal supplements is an evolving challenge, which requires consideration of the safety profile of alternative medicines. Various bioactive constituents of garlic inhibit platelet aggregation *in vitro* (3–9). Interference with the biosynthesis of prostaglandins via inhibiting cyclooxygenase 1, comparable to aspirin, and direct interaction with the fibrinogen receptors have been reported as the target mechanisms for garlic-induced platelet inhibition (6,9). *In vivo*, extracts of garlic inhibited platelet aggregation, adhesion to fibrinogen, and thromboxane B_2 secretion (10–13). Garlic increased the risk for postoperative bleeding and spinal hematoma (14–17). Current trends in anesthesia practice suggest avoiding any garlic consumption 7 days before surgery (especially if postoperative bleeding is a particular concern) (1,2,18–20) even though the extent to which dietary doses of garlic influence platelet aggregation remains unknown.

Full-flavored dishes containing garlic are typical for the Southern European cuisine and have become more common worldwide. Making dietary rules, which preclude the ingestion of such dishes, may unnecessarily complicate perioperative care. To clarify this issue, we tested the effect of raw garlic at a dose of 4.2 g prepared in Greek tsatsiki on platelet function using point-of-care monitoring devices sensitive to cyclooxygenase I-inhibition and platelet adhesive capacity.

METHODS

After IRB approval and informed consent 23 healthy adult female and male volunteers were investigated in a randomized, crossover, observer-blinded, placebo-controlled study. All volunteers had not taken any medication for 14 days and were required to obey dietary regulations, which precluded the ingestion of

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substances with known or suspected platelet-inhibiting side effects, such as raw garlic, onion, ginger, and ginkgo (18). After overnight fasting, 18 volunteers received test ingestions consisting of Greek tsatsiki (yogurt, quark, cucumber, salt, pepper, and dill) with 4.2 g raw garlic plus one Viennese bread roll (verum), or Greek tsatsiki (yogurt, quark, cucumber, salt, pepper, and dill) without garlic plus one Viennese bread roll (placebo). Garlic bulbs were purchased locally from the vegetable market. Doses of garlic in traditional Greek tsatsiki approximate 2.5 g. The dose of 4.2 g of garlic was chosen because it exceeds the common amount and the pungent, but not over-powering, taste was well tolerated by our pilot volunteers.

To ensure recovery of potentially irreversibly inhibited platelet function, the time interval between the two test ingestions was 10 days. The sequence of test ingestions was randomly assigned using a computer-generated random table. Research subjects may have tasted the characteristic flavor of raw and freshly crushed garlic and were, therefore, not defined as blinded to the test ingestion. Observers, however, were blinded to the test ingestion. A dish with raw instead of boiled garlic was chosen, because boiled garlic failed to show significant effects on platelets in previous studies (9). Volunteers were allowed to eat according to the dietary regulations beginning 3 h after the test ingestion.

The effect of prolonged garlic ingestion at large amounts was assessed in five additional volunteers consuming Greek tsatsiki with 4.2 g raw garlic daily for 1 wk.

Five hours after garlic intake, significant increases in rheological and antiatherosclerotic effects were reported in pharmacological human studies (21). Accordingly, blood withdrawal was performed before and 5 h after test ingestions in the crossover trial, as well as before and after the last test ingestion in the long-term trial. Atraumatic venipuncture was performed without stasis from an antecubital vein using a 21-gauge butterfly needle. The first 3 mL of blood was always discarded.

The agonists arachidonic acid, collagen, and epinephrine were found to be indicative of irreversible platelet inhibition induced by garlic principles in other studies (3–13). Accordingly, the following monitoring methods were chosen. For assessment of platelet function analyzer (PFA)-closure times 800 μL of whole blood drawn into one 4-mL Vacuette™ tube containing 3.8% trisodium citrate (Greiner, Kremsmünster, Austria; citrate–blood = 1:9) was analyzed in the PFA-100®, (Dade, Miami, FL) using epinephrine or collagen as agonists. The blood sample is aspirated through a capillary with a coated membrane and then passes through an aperture. In response to the stimulation by collagen and epinephrine, present in the coating, and the shear stress at the aperture, platelets adhere to and aggregate on the collagen surface. The platelet plug ultimately occludes the aperture. The time required to obtain full occlusion of the aperture is defined as the PFA-closure time (normal range <165 s) and is dependent upon platelet function, platelet counts, von Willebrand factor levels, and platelet adhesive capacity (22).

Platelet aggregometry was performed with the new impedance aggregometer Multiplate® (Dynabyte, Munich, Germany) in whole blood drawn into one 3.5-mL DTI-tube (direct thrombin inhibitor blood collection tube; Dynabyte, Munich Germany; melagatran 14 μg/mL). In impedance aggregometry, two electrodes are immersed in 300 μL of whole blood that is continuously stirred. In response to arachidonic acid (0.5 mM) or collagen (3.2 μg/mL), platelet aggregates attach to the electrodes, increasing the impedance between them, which is then transformed into arbitrary aggregation units and plotted against time (23). Values are reported as area under the aggregation curve (AUC; aggregation units · min).

The Platelet Mapping™ assay was performed using the Thrombelastograph® Hemostasis Analyzer (Hemoscope Corporation, Niles, IL). In this assay, heparin-anticoagulated (18 IU/mL) whole blood is clotted by a reptilase-factor XIIIa activator mixture. The maximum amplitude of the clotting trace (MA_0) generated is proportional to the magnitude of platelet activation. The MA_0 is compared with the MA_{AA} in clotted blood with additional arachidonic acid activation, and the MA_K of a standard kaolin-activated aliquot of citrated blood:

$$MA\,\% = 100 \times MA_{AA} - MA_0/MA_K - MA_0$$

(normal range $\leq 20\%$)

This assay has been recommended for monitoring cyclooxygenase I-inhibition by aspirin (24).

All instruments were calibrated according to the manufacturer's standards, and all tests were conducted on duplicate samples and completed within 2 h to ensure maximum platelet function.

A series of *in vitro* experiments was performed to prove the sensitivity of the assays to garlic-induced platelet inhibition. Dry garlic powder in the herbal medicine Nutrico® Knoblauch 500 (Nutrisan GesmbH, Vienna, Austria) with a standardized content of 167 mg garlic concentrate was dissolved in normal saline 0.9%. Blood samples (300 μL) were incubated for 30 min with either 20 μL of dissolved garlic powder after sterile filtration (0.2 μm) at a final concentration of 0.281 mg/mL, or 20 μL normal saline 0.9% (control). *In vitro* experiments were performed in duplicates in blood obtained from the first four volunteers before test ingestion. Since pharmacokinetics and plasma concentrations of active garlic moieties have not been determined, the final concentration of garlic was chosen by assuming distribution of the recommended upper dose of garlic powder in plasma volume.

Table 1. Platelet Function Parameters After Single Dose of Garlic

	Before placebo	After placebo	*P*	Before 4.2 g garlic	After 4.2 g garlic	*P*
ASPI-aggregation (normal: 361–892 AUC)	837 (140)	813 (139)	0.796	751 (106)	778 (151)	0.276
COLL-aggregation (normal: 546–1134 AUC)	731 (143)	685 (216)	0.877	703 (201)	711 (216)	0.687
PFA-closure time (s) (normal: <165 s)	137 (21)	145 (26)	0.836	139 (39)	144 (31)	0.448
MA-reduction (%) (normal: ≤20%)	4.2 (6.4)	2.6 (4.0)	0.272	7.5 (6.9)	3.2 (4.4)	0.069

There were no significant differences between the two test ingestions. Results are presented as mean (SD), Wilcoxon test.

AUC = area under the aggregation curve (aggregation units · min); ASPI = arachidonic acid-induced aggregation; COLL = collagen-induced aggregation; PFA = Platelet Function Analyzer PFA-100; MA = thrombelastographic maximum amplitude.

Table 2. Platelet Function Parameters After Repeated Doses of Garlic

	Before garlic	After 4.2 g garlic daily for 1 wk	*P*
ASPI-aggregation (normal: 361–892 AUC)	882 (79)	879 (76)	0.893
COLL-aggregation (normal: 546–1134 AUC)	892 (293)	655 (220)	0.893
PFA-closure time (s) (normal: <165 s)	130) (31)	150 (30)	0.138
MA-reduction (%) (normal: ≤20%)	7.5 (11.9)	7.6 (5.4)	0.500

There were no significant differences between measurements performed before and after long-term exposure to garlic. Results are presented as mean (SD), Wilcoxon test.

AUC = area under the aggregation curve (aggregation units · min), ASPI = arachidonic acid-induced aggregation, COLL = collagen-induced aggregation, PFA = Platelet Function Analyzer PFA-100, MA = thrombelastographic maximum amplitude.

Statistical Analysis

Data are expressed as mean ± SD. Differences in baseline values and differences before and after each test ingestion were analyzed by Wilcoxon test. $P < 0.05$ was considered statistically significant.

RESULTS

Twenty-three volunteers at the mean age of 29 ± 8 yr, with a mean weight of 73 ± 14 kg and a mean height of 174 ± 9 cm were included. Platelet counts were within normal range (264 ± 64 G/L).

Mean values of platelet function were within normal range throughout the whole study. Neither verum (4.2 g raw garlic) nor placebo (no garlic) inhibited platelet function in the crossover trial in any point-of-care monitoring test used (Table 1). Repeated ingestion of raw garlic also had no inhibiting effect on platelet function (Table 2).

In our *in vitro* experiments, garlic powder inhibited arachidonic acid-induced platelet aggregation by 46% ± 16%, prolonged epinephrine-induced PFA-closure times by 45% ± 44%, and impaired arachidonic acid-induced platelet function assessed by the Platelet Mapping assay by 193% ± 4%. No changes were observed in control samples diluted with saline 0.9%.

DISCUSSION

This study was undertaken to quantify the effect of raw garlic at a dietary dose on platelet function. Our results show that single consumption of fresh garlic up to 4.2 g (approximately 1–2 garlic cloves) has no inhibitory effect on platelet function in healthy volunteers. Measurements were performed 5 h after ingestion because at this time point, peak responses in rheological and antiatherosclerotic effects were reported in previous human studies (21). Our results on the effects of continuous ingestion of 4.2 g garlic daily for a week confirmed the absence of relevant platelet inhibition.

In contrast to our results from investigating the effect of raw garlic, several garlic powders and extracts, derived from garlic or processed garlic oils, (including diallyl thiosulfinate (allicin), alliin, ajoene, methyl allyl trisulfide, diallyl trisulfide, dimethyl trisulfid, vinyl disulfide, and nonsulfur steroid saponins) have been shown to exhibit antiaggregatory effects (3–13). Because of garlic's chemical complexity, however, diverse processing methods yield preparations with differing efficacy and chemical composition of bioactive garlic constituents. Therefore, differences in the amount and type of bioactive garlic components that eventually reach the blood platelets in the circulation may account for the discrepancy between our results using raw garlic cloves and previous studies using processed garlic (3–13). The bioavailability of most inhibitory organosulfur compounds of garlic is low because of limited absorption from the intestinal tract and rapid inactivation in the bloodstream (25). Processing increases the potency and bioavailability of organosulfur compounds compared with ingestion of raw garlic.

Not only differences in the use of raw versus processed garlic, but also differences in garlic dosage need to be considered when comparing our results to previous reports. The only available previous study investigating the *in vivo* effect of raw garlic shows that intake of 10 g of fresh garlic daily for 2 mo increased clotting times from 4.15 to 5.02 min (26). In our study, a dose of 4.2 g of garlic was chosen which is closer to the common amount in full-flavored dishes without an over-powering taste. Together, these data indicate that raw garlic ingestion at 4.2 g does not lead to an increase in antiplatelet bioactive garlic components above a critical level in systemic circulation. High

doses of garlic can cause diarrhea, burning sensations, and garlic odor of the breath and skin (27). Although 10 g of raw garlic consumed daily for 2 mo induced no adverse events (26), a case report described the association of excessive amounts of raw garlic (four cloves per day) with spontaneous spinal hematoma in a nonagenarian (17).

When extrapolating the reported antiaggregatory effect of processed garlic products (3–12) and one single case report (17), current trends in preoperative practice suggest avoiding any type of garlic consumption before surgery (1,2,18–20). The present results, however, demonstrate that raw garlic at a dose of 4.2 g prepared in a Mediterranean dish does not affect measures of platelet function in healthy volunteers. Accordingly, giving dietary regulations in perioperative care, which preclude ingestion of such dishes with crushed or finely chopped garlic, is not recommended. Patients do not have to abstain from a preoperative dinner containing garlic.

Garlic changes the characteristics of its intrinsic chemistry according to the method of processing. Irritating and oxidizing compounds can be extracted with alcohol, milk, vinegar, or soy sauce before use, as is done by some cultures. Cooking whole or coarsely chopped garlic cloves destroys volatile and chemically unstable thiosulfinates because of evaporation and conversion. Accordingly, boiled garlic in many national dishes is not likely to exert any effect on platelet function.

Raw garlic constituents may enhance the effect of antiplatelet drugs, anticoagulants, or analgesic drugs (28–30). However, processed garlic did not increase bleeding events in patients receiving oral anticoagulation therapy (29). The authors concluded that processed garlic is unlikely to be a potent antiplatelet agent and that garlic is beneficial, especially in patients with a high-risk thrombosis history. Further, there are no reports that directly relate the occurrence of bleeding events to co-medication of antiplatelet drugs and garlic consumption. Nevertheless, it may be prudent to identify patients with inherited or acquired platelet dysfunctions and raw garlic consumption during the perioperative period and to closely observe coagulation function. Further *in vivo* studies using sensitive point-of-care platelet function tests are warranted to investigate the antiaggregatory effects caused by processed garlic supplements and other herbal medicinal products at clinically relevant dosages in patients at risk for bleeding.

Garlic extracts, synthesized thiosulfinates, and the garlic derivative ajoene inhibited platelet aggregation *in vitro* in platelet-rich plasma and whole blood (3–9). Our *in vitro* experiments confirm that the whole blood point-of-care platelet function tests we used (Multiplate, PFA-100, and Platelet Mapping assay) permit the detection of platelet dysfunction induced by garlic extracts. Platelet inhibition induced by garlic can be detected by using the agonists arachidonic acid, collagen, and epinephrine used in our study. Platelet receptor expression using flow cytometry was not determined in the present study, because point-of-care platelet function monitoring appears to be more appropriate for preoperative diagnostic screening than a method predominantly used for scientific purposes. The PFA-100 has been recommended for preoperative platelet function screening because it sensitively detects aspirin's effects as well as defects, e.g., due to von Willebrand syndrome (31). Whole blood platelet aggregometry (Multiplate, Platelet Mapping assay) permits detection of aspirin and clopidogrel's effects (when using adenosine diphosphate as agonist) (23,24). Testing in whole blood allows for more physiological testing when compared with Born aggregometry, which is performed in platelet-rich plasma or on isolated platelets. Whole blood platelet function tests still require the addition of agonists and anticoagulation *ex vivo* which, by itself, may modify the platelet's response. At present, there is no monitoring test equipment available that allows for investigation of the interaction between endothelial blood vessels and platelets. Accordingly, the rheological effects of garlic are not reflected by the methodology but may contribute to clinical bleeding.

In summary, platelet function is not impaired by oral consumption of Greek tsatsiki containing raw garlic in any point-of-care monitoring test we used. Dishes containing raw garlic are unlikely to increase the risk of perioperative bleeding. Therefore, avoiding dietary raw garlic in socially acceptable doses is not necessary preoperatively.

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