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ORIGINAL ARTICLE

Interaction study between antiplatelet agents, anticoagulants, diabetic therapy and a novel delivery form of quercetin

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ABSTRACT

BACKGROUND: In this pilot non-interference clinical study we evaluated possible interactions between Quercetin Phytosome® (Quercefit™), an innovative delivery form of quercetin, and antiplatelet agents, anticoagulants, and anti-diabetic therapy in otherwise healthy subjects.

METHODS: Interaction with antiplatelet therapy was assessed through the bleeding time (BT) test in 30 patients treated with acetylsalicylic acid, ticlopidine or clopidogrel before and after 10 days of supplementation with Quercetin Phytosome®. Interaction with anticoagulants was evaluated by measuring the International Normalized Ratio (INR) in 20 patients using warfarin or dabigatran before and after 20 days of supplementation with Quercetin Phytosome®. Lastly, glycaemia and glycated hemoglobin were measured in 12 diabetic patients treated with metformin and restricted diet before and after 20 days of supplementation with Quercetin Phytosome®.

RESULTS: After 10 days of supplementation no significant difference was observed in mean BT in patients treated with acetylsalicylic acid, ticlopidine or clopidogrel at standard dosages. Similarly, after 20 days of supplementation, the INR level among patients assuming warfarin or dabigatran was not statistically different from baseline. Lastly, no statistically significant difference in mean levels of glycaemia and glycated hemoglobin was reported before and after 20 days of complementary administration of Quercetin Phytosome® in diabetic patients treated with metformin and restricted diet.

CONCLUSIONS: Quercetin Phytosome® does not alter the antiplatelet activity of the most common antiplatelet agents, has no impact on the INR values in stable patients treated with warfarin or dabigatran, and does not influence the metabolic control of diabetic patient treated with metformin.

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KEY WORDS: Quercetin - Anticoagulants - Cardiovascular diseases.

During the last century, rising living standards and advances in healthcare and medicine have led to a progressive growth and ageing of the global population, with a consequential spreading of polypharmacy.[1-3] Among the elderlies, cardiovascular and metabolic disorders represent the most prevalent conditions, due to the increased health-related risks associated with old age.[4, 5] As a result, anticoagulant and antiplatelet agents are frequently prescribed to reduce the risk of cardiovascular and cerebrovascular conditions.[6, 7] Metabolic diseases such as diabetes are

also on the rise; according to the World Health Organization the global prevalence of diabetes has nearly doubled since 1980, currently reaching 8.5% of the adult population.[8]

Furthermore, complementary and alternative approaches such as foods and herbs have gained increasing popularity during the last decades, thanks to their beneficial effects in multiple diseases.[9] It is crucial to know how these interventions interact with standard synthetic drugs commonly used in the same target populations, to prevent any possible harmful effect. This is extremely important especially for anticoagulants and antiplatelet agents, as any deviation from their therapeutic window can lead to safety concerns due to excessive bleeding or conversely to excessive coagulation and consequential thrombosis.[10] Some interactions have already been detected; for example a variety of herbal medicines and nutrients seem to affect dietary intake of vitamin K, thus altering the risk/benefit ratio of vitamin K agonists (VKAs).[11] Numerous herbal medicines have also been identified that could potentially affect the pharmacokinetic and pharmacodynamic properties of anti-diabetic drugs.[12]

Quercetin is a plant flavonol used as herbal remedy thanks to its recognized beneficial effects on human health.[13] It can be found in many fruits, vegetables, leaves, and grains; also red onions and kale are common foods containing appreciable content of quercetin. The bioavailability of quercetin in humans is low and highly variable (0-50%), and it is rapidly cleared with an elimination half-life of 1-2 hours after ingesting quercetin foods or supplements. Following dietary ingestion, quercetin undergoes rapid and extensive metabolism that makes the biological effects suggested by *in vitro* studies unlikely *in vivo*.[13]

Quercetin Phytosome® is an innovative delivery form of quercetin formulated in a specific food grade delivery system to enhance its bioavailability.[14-16] This novel proprietary phospholipids based delivery system is standardized to contain ≥34.0% ≤42.0% of quercetin by HPLC with demonstrated improved solubility in simulated gastrointestinal fluids and 20-fold improved absorption in a recent human pk study (publication ongoing).

Materials and methods

Patients

In this pilot non-interference clinical study, we evaluated the effect of Quercetin Phytosome® — used as an anti-inflammatory, anti-fatigue and anti-oxidant agent in otherwise healthy subjects — in subjects on antiplatelet or anticoagulant therapy, and in diabetic patients treated with metformin and on restricted diet. Patients treated with any other additional medication were excluded from the study.

Interaction between Quercetin Phytosome® and antiplatelet therapy was assessed by measuring platelet function *in vivo* through the bleeding time (BT) test in patients under chronic antiplatelet therapy with acetylsalicylic acid (Cardioaspirin®), ticlopidine (Ticlid®) or clopidogrel (Plavix®). The BT was evaluated before and after 10 days of supplementation with Quercetin Phytosome® (2 tablets/day, corresponding to 200 mg/day of quercetin).

Interaction between Quercetin Phytosome® and anticoagulants was assessed in patients using warfarin (Coumadin®) or dabigatran (Pradaxa®) for previous venous thrombosis at doses adequate to keep an International Normalized Ratio (INR) level of about 3. The INR level was evaluated before and after 20 days of supplementation with Quercetin Phytosome® (2 tablets a day, corresponding to 200 mg/day of quercetin).

The effect of Quercetin Phytosome® on metabolic control in diabetic patients was evaluated by measuring levels of glycaemia (fasting blood sugar test) and glycated hemoglobin before and after 20 days of supplementation with Quercetin Phytosome® (2 tablets a day, corresponding to 200 mg/day of quercetin) in diabetic male patients using metformin (twice daily for at last 1 year before the study) and following a restricted diet.

The study was approved as an observational registry by the Ethics Committee of the IAPSS (International Agency For Pharma Standard Supplements) (PSS-17/212 7G).

The *in vivo* BT

The BT is defined as the time required for spontaneous bleeding to stop after an incision is made

into the skin, generally on the forearm anterior surface. The bleeding test was performed with 2 small horizontal skin cuts (3 mm); excess blood was removed using a filter paper and the time was recorded until bleeding stop.[17] Environmental parameters such as room temperature (22 °C) were adjusted to favor BT reliability.[18, 19] Of note, BT values usually range from 2 to 10 minutes in normal subjects, and can exceed 30 minutes in patients with severe platelets defects.

Statistical analysis

Descriptive statistics were used to analyze patients' demographic characteristics and baseline measurements. The Mann-Whitney U-test was used to compare BT before and after supplementation with Quercetin Phytosome®. All statistical analyses were performed with SPSS for Windows version 22 (Statistical package for Social Sciences, IBM Inc.), and the significance level was set at 0.05.

Results

Interaction between antiplatelet agents and Quercetin Phytosome®

The antiplatelet interaction study included 30 patients in stable conditions after at least 2 years of antiplatelet management at standard dosages, in line with the British National Formulary (BNF). Mean age was 55 years old and Body Mass Index ranged from 22 to 36; 17 subjects were males. Antiplatelet therapies consisted of acetyl-salicylic acid 100 mg/day, ticlopidine 250 mg/day or clopidogrel 75 mg/day; each treatment group comprised 10 patients. Mean BTs values were within normal ranges in all the groups both before and after supplementation; no significant difference was reported in mean BTs before and after 10 days of treatment with Quercetin Phytosome® (Figure 1).

Interaction between anticoagulants and Quercetin Phytosome®

As summarized in Table I, 10 patients assumed warfarin and 10 dabigatran; the two groups comprised 6 females each. Before Quercetin Phytosome® supplementation, mean INR was close to 3 in both groups and platelets were within normal ranges; after 20 days of Quercetin Phytosome® treatment no statistically significant changes was recorded in INR, nor in platelets level, that remained normal (Table I).

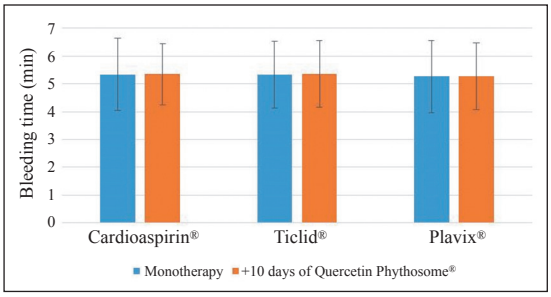

Figure 1.—Bleeding times (BTs) in patients on antiplatelet therapy, before and after 10 days of supplementation of Quercetin Phytosome®.

TABLE I.—*Mean INR levels in patients on anticoagulant therapy, before and after 20 days of supplementation with Quercetin Phytosome®.*

Anticoagulant	Patients	INR (mean; SD)	Platelet
Coumadin®	10	2.92; 0.3	NV
Coumadin® + Quercetin Phytosome®		2.93; 0.2 NS	NV
Praxada®	10	2.94; 0.3	NV
Praxada® + Quercetin Phytosome®		2.93; 0.33 NS	NV

INR: International Normalized Ratio; NS: not statistically significant; NV: normal value; SD: standard deviation.

Interaction between diabetic therapy and Quercetin Phytosome®

Twelve diabetic male patients were included in this observational study; mean age was 53.4 (Standard Deviation [SD] 3). No interaction was observed between metformin and Quercetin Phytosome®: indeed no statistically significant difference in mean levels of glycaemia and glycated haemoglobin was reported before and after 20 days of complementary administration of Quercetin Phytosome® (Figure 2A, B).

Discussion

Interactions between herbal medicines and synthetic drugs exist and can have serious clinical consequences.[20] This is especially true for anticoagulants and antiplatelet agents, for which

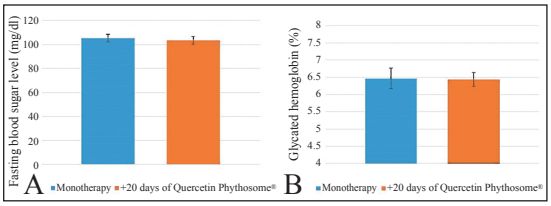

Figure 2.—Mean levels of glycaemia (fasting blood sugar test) (A) and glycated hemoglobin (B) at baseline (T0) and after 20 days (T20) of supplementation with Quercetin Phytosome® in diabetic patients on metformin and restricted diet.

multiple interactions with common herbal remedies have already been identified.[21] Of note patients on anticoagulants seem to have a higher risk of potentially harmful interactions compared to those treated with other cardiovascular drugs.[22] Diabetic patients may also have a higher risk of herb-drug interactions: indeed many of these patients are known to combine their mainstream treatment with natural compounds with antidiabetic properties, and various medicinal plants have been shown to alter the activity of commonly prescribed anti-diabetics, eliciting additive effects or causing safety concerns.[12]

In this pilot registry study, Quercetin Phytosome®, at the dosages routinely used as complementary support in otherwise healthy subjects, showed no pharmacological interaction with antiplatelet agents or anticoagulants, and had no impact on BT and INR after at least 10 days of supplementation. These results provide some guidance to health care professionals on the use of Quercetin Phytosome® in patients assuming antiplatelet agents or anticoagulants, suggesting that no adjustment in the standard cardiovascular therapy is required in case of concomitant supplementation with Quercetin Phytosome®. This information is particularly important considering that the drugs tested in this study (*i.e.* acetyl salicylic acid, warfarin) are extremely common among the general population. Of note, this study also suggests the lack of interactions between Quercetin Phytosome® and dabigatran, a novel oral anticoagulant (NOACs) that directly inhibits factor IIa. This new class of drugs, developed since 2000s and including also Xa inhibitors (*e.g.* rivaroxaban or apixaban), should be carefully taken into consideration in future non-interference studies between anticoagulants and foods, supplements or plant extracts.[7]

Similarly to the results obtained on anticoagulants and antiplatelet agents, Quercetin Phytosome® showed no clinically relevant interference with metformin in diabetic patients, who maintained their metabolic control after 20 days of supplementation with no alteration in the levels of glycaemia (fasting blood sugar test) or glycated hemoglobin. These findings support the use of Quercetin Phytosome® in diabetic patients, with no impact and no need for adjustments in the anti-diabetic therapy.

Conclusions

The results of our study suggest that Quercetin Phytosome® supplementation does not alter the antiplatelet activity of the most common antiplatelet agents, nor has any impact on the INR values in stable patients treated with warfarin or dabigatran. Similarly, metformin regimen in diabetic patients does not need to be adjusted in case of complementary treatment with Quercetin Phytosome®, thanks to lack of herb-drug interactions.

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Conflicts of interest.—Antonella Riva is an Indena employee. Luca Giacomelli is an Indena consultant. The other authors declare no conflict of interest directly relevant to this study.

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