Mini Review

Warfarin: Looking Beyond Vitamin K in Diet

Navneet Attri, Lenora Farnam-Fard[1]

Pacific Inpatient Medical Group, Sutter Santa Rosa Regional Hospital, Department of Medicine, Sutter Santa Rosa Regional Hospital, [1]Department of Pharmacy, Sutter Santa Rosa Regional Hospital, Santa Rosa, CA, USA

Abstract

Warfarin has been widely used for its anticoagulant properties. It has a narrow therapeutic range with complex interactions with various dietary products, herbal supplements, and with other medications. We recently encountered a case of warfarin coagulopathy in a patient that had been on stable doses of warfarin since 2011 with successful maintenance of international normalized ratio in the therapeutic range. By the process of elimination, the cause was attributed to the patient's recent inclusion of pineapple papaya smoothies in her diet. This study highlights the importance of detailed history taking with a focus on diet changes and supplements in patients on warfarin. Warfarin has an extensive list of interactions with prescription and over-the-counter medications, various vegetables, fruits, and herbal supplements through an effect on warfarin metabolism by cytochrome 450 enzymes. While it is a well-known fact that green leafy vegetables diminish warfarin therapeutics due to their high Vitamin K content, warfarin interactions with fruits are less well known. The focus of this article is a review of the literature about the plausible interactions of pineapple and papaya with warfarin. We have briefly touched on the interactions of warfarin with other fruits.

Keywords: Fruit interactions, pineapple, papaya, warfarin

Introduction

A 50-year-old female with a past medical history of St. Jude's mechanical mitral valve on warfarin since 2011, hypertension, and hyperlipidemia presented to the Emergency Department of our hospital with hematuria, skin bruising, hemoperitoneum, and left leg swelling suspicious of hematoma. Blood work was remarkable for international normalized ratio (INR) 14.7, partial thromboplastin time 167, and hemoglobin 10.8. Platelets, liver, and renal functions were normal. The patient reported stable INR since 2011. This was confirmed through our access to her INR by means of an integrated electronic medical record with her primary care physician and coumadin clinic. She denied any recent antibiotics, new medication, new supplements, or herbal products and denied any recent change in her intake of green vegetables. Two weeks ago, she had started drinking a smoothie for weight loss every other day. The ingredients in the smoothie were one cup of pineapple, one cup of papaya, almond milk, half a banana, and occasionally an apple.

Methods

We did a PubMed search with keywords: and warfarin, bromelain, papain, and papaya; the search was further refined using the words: pineapple, warfarin, and fruit interactions which generated 83 articles

Discussion

Warfarin is metabolized by the enzymes produced by liver microsomes called cytochrome P450 which is also responsible for the metabolism of many other drugs.[1,2] There are six enzymes in this family: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 which are responsible for 90% of oxidation processes.[3,4] The S-enantiomer of warfarin (approximately 2–5 times more potent than the R-isomer) is primarily metabolized by CYP2C9 and to a lesser degree CYP3A4.[2,5-8] The R-enantiomer is metabolized by CYP1A2 and CYP3A4.[4,5] The anticoagulant efficacy of warfarin is affected mainly when S-warfarin is metabolized by CYP2C9 and to a lesser extent by CYP3A, both located in

Address for correspondence: Navneet Attri, Sutter Santa Rosa Regional Hospital, 30 Mark West Springs Road, Santa Rosa 95403, CA, USA.
E-mail: attrin@sutterhealth.org

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the intestinal epithelium.[1] Other enzymes that likely play a role in the metabolism of warfarin are CYP2C8, CYP2C18, and CYP2C19.[5-7]

Warfarin, thus, remains susceptible to multiple interactions with other medications that utilize the CYP450 system. In addition, fruits, vegetables, and nutritional supplements can inhibit the various enzymes involved in warfarin metabolism, mostly by inhibition of CYP2C9 activity.[8] A review of the literature suggested the plausible role of pineapple and papaya in contributing toward our patient's coagulopathy.

In a study by Hidaka *et al*.,[9] the effect of various citrus fruits and tropical fruits on CYP29 activity of human liver microsomes was studied *in vitro*. The addition of 25 µL pineapple juice resulted in almost complete inhibition of CYP2C9 activity. They also studied the inhibitory effect of bromelain, a mixture of cysteine proteases found in the pineapple fruit and stem.[10] Bromelain, at a concentration of 1.2 µg/ml was found to strongly inhibit intestinal CYP2C9 from where it is absorbed.[9] Furthermore, the inhibitory effects of pineapple juice and bromelain on CYP2C9 were entirely blocked by a cysteine protease inhibitor E-64.[9] Ultrafiltration and heat treatment of pineapple juice to remove its proteolytic activity led to the loss of pineapple's CYP2C9 inhibitory activity indicating bromelain is the principal ingredient of pineapple juice responsible for its inhibitory effects.[9] The inhibition of CYP2C9 by pineapple juice was noted in a dose-dependent manner *in vitro,* and the study hypothesized that the inhibition was likely to occur *in vivo* as well.[9]

Pineapple's interaction with warfarin seems to be mediated primarily by bromelain.[9,10] Bromelain has two main sources: fruit bromelain extracted from pineapple fruit and stem bromelain extracted from inedible pineapple stem.[9,10] Stem bromelain is economical to produce and used in nutrition supplements.[11] A web search for bromelain supplements reveals a huge market for these over-the-counter supplements for reducing pain, ecchymosis and swelling after surgery, wound debridement, arthritis, musculoskeletal injuries, slowing clotting, shortening labor, and helping the body get rid of fat. Bromelain's primary mechanism of action is inhibition of the CYP2C9[4,9] leading to potentiation of the effects of warfarin. Bromelain also has its own anticoagulant and antiplatelet effects. Bromelain is a potent inhibitor of platelet aggregation, both *in vivo* and in *in vitro* by reducing ADP-induced platelet aggregation.[1,12,13] In a study by Metzig *et al*.,[14] preincubation of platelets with bromelain (10 µg/ml) completely prevented thrombin-induced platelet aggregation and platelet adhesion to endothelial cells. In addition, bromelain promotes fibrinolysis both *in vitro* and *in vivo* by inhibition of thrombin synthesis.[1,12,13] Inhibition of thrombin inhibits the conversion of soluble fibrinogen to insoluble fibrin, thus interfering with platelet activation and clot stabilization.[15]

Papain, a cysteine proteinase in the papaya, also has been associated with an increased INR. The exact mechanism is not known, but weak inhibition of CYP2C9 is suggested.[5,9] It is believed that papain has sulfhydryl proteases that act like bromelain regarding coagulation.[5,16,17] At lower concentrations, bromelain seems more effective in reducing thrombin-induced platelet aggregation in bovine epithelial cells as compared to papain. However, at higher protease concentrations, bromelain and papain have proven to be equally effective.[14] Notably, there is a mention of higher concentration of papain in unripe papaya as compared to the ripe fruit that can lead to serious bleeding.[5,18] On web search, unripe papaya is commonly used in several salads and has been promoted in over-the-counter supplements for boosting immunity, improving skincare, relief from menstrual cramps, protecting against heart diseases, and regulating digestion.

In a comprehensive review by Norwood *et al*.,[5] they examined other fruits that have been mentioned to have an interaction with warfarin such as pomegranate juice, avocado, mango, and grapefruit juice.[5] The mechanisms of interaction of these fruits with warfarin are complex and varied. The most well-studied fruits have been grapefruit and cranberry. Cranberry juice has been reported to cause significant inhibition of CYP2C9 and CYP3A4 in several clinical reports,[5,19,20] but no significant effects of cranberry juice were noted in two randomized, double-blind, placebo-controlled studies.[21,22] Similarly, flavonoids found in grapefruit juice can likely inhibit the hepatic and to a lesser extent intestinal CYP3A4 in a dose-dependent manner,[23,24] thus increasing the effects of warfarin if consumed in large amounts. In laboratory studies, pomegranate juice inhibits CYP2C9 found on the intestinal epithelial cells.[8,25-27] and inhibits CYP3A4.[26,27] Kiwi fruit, through its cysteine proteinase, actinidin, has been noted to have weak inhibition on CYP2C9 *in vitro*.[9] Avocado is rich in Vitamin K[28] and can reduce the therapeutic efficacy of warfarin. Mango with high amount of Vitamin A (retinol) may inhibit CYP2C19, involved in the metabolism of warfarin's R-isomer,[29] and increase the warfarin effect.

The plausible mechanisms of Warfarin-fruit interactions are summarized in the Table 1.

Conclusion

Our patient had maintained her INR in the therapeutic range since 2012 per our review of the electronic medical records

Table 1: Possible mechanisms of fruit interactions with warfarin

Fruit/fruit juice	Possible mechanism of warfarin-fruit interaction
Pineapple	Inhibition of CYP2C9
Papaya	Inhibition of CYP2C9
Cranberry	Inhibition of CYP3A4 and CYP2C9
Grapefruit	Inhibition of CYP3A4
Pomegranate	Inhibition of CYP2C9 and CYP3A4
Kiwi	Inhibition of CYP3A4 and CYP2C9
Mango	? Inhibition of CYP2C19
Avocado	Vitamin K in avocado may inhibit Vitamin K and increase INR

References are in the body of the text

until recently when she started taking fruit smoothie. Due to the lack of any other explanation for her coagulopathy, it is highly probable that the pineapple and papaya in her smoothie played a role in the causation of her coagulopathy. We speculate that there might have been a synergistic effect of the combination of pineapple and papaya in CYP2C9 inhibition. We are not aware of any studies that have investigated the synergistic effects of fruits and vegetables in inhibition of cytochrome P450 enzymes.

Even though warfarin is being phased out by novel oral anticoagulants, it remains the anticoagulant of choice in the setting of prosthetic valves and some other conditions. Hence, it is extremely important for providers to caution patients about warfarin's complex interactions periodically. For recent labile INR in previously stable patients, detailed history with respect to any changes to medications, diet, or addition of supplements should be taken.

Our case study is limited in its scope due to the lack of scientific research to support it. Most *in vitro* results could not be replicated *in vivo*. Multiple enzymes and nutrients in fruits and vegetables can make attribution of a physiological effect to one enzyme or nutrient extremely challenging. The exact dose and duration after which a potentially useful fruit product or supplement can interact with medication are not known. Some nutrients can act synergistically and likely compound their drug interactions.

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Conflicts of interest

There are no conflicts of interest.

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