IECN 2024 Conference

The 4th International Electronic Conference on Nutrients

16–18 October 2024 | Online

MDPI

The Impact of Berry Fruits from the *Vaccinium* Genus on Drug-Metabolizing Enzymes: A Systematic Review

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INTRODUCTION & AIM

Plants of the *Vaccinium* genus are low-branched, deciduous shrubs that belong to the Ericaceae family. They produce berries rich in various phenolic compounds, including quercetin, myricetin, isorhamnetin, tannins, ellagitannins, phenolic acids, and anthocyanins. The most abundant bioactive compounds in these berries are anthocyanins, which give the fruits their distinctive dark blue color. These metabolites comprise anthocyanin aglycones, sugar moieties, and acyl groups.

This study aimed to systematically review clinical research on the effects of berry fruits on drug-metabolizing enzyme activity.

The positive health benefits of berry fruits have increased the production and consumption of dietary supplements rich in blueberry extract. However, high doses of berry extracts from the *Vaccinium* genus may cause adverse effects, including potential interactions with other drugs. Blueberry extracts can influence drug behavior and efficacy by altering the activity of drug-metabolizing enzymes, which convert lipophilic drugs and other xenobiotic compounds into polar products for more straightforward elimination from the body. Such interactions between berry fruit compounds and medications can pose risks to patients.

METHOD

To ensure the transparency of the research conducted, the review was prepared following PRISMA guidelines (Page et al., 2021). An electronic-based search was performed in the scientific libraries Cochrane, Ebsco, PubMed, Embase, Scopus, and Web of Science. Searches comprised a combination of MeSH terms and keywords, applying quotes and field tags with BOOLEAN operators. For all databases, four primally exclusion steps were determined: 1. keywords (*vaccinium* or *blueberry* or *bilberry or cranberry*) AND ("*drug interactions*" or "*medicines interactions*"), 2. Publication years (1993-2022), 3. Language (English), 4. Publication type (article).

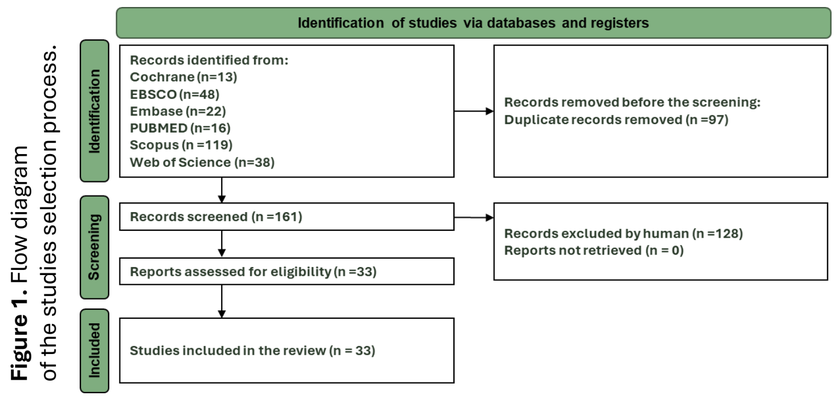

Figure 1. Flow diagram of the studies selection process.

The screening was made in the areas: Title, Abstract, Keywords (Cohrane, Embase, Ebsco, PubMed, Scopus), and Topic (Web of Science). The search and selection process was performed by two reviewers working independently in parallel (Figure 1). Initial searches returned 256 results, and after removing duplicates, 161 peer-reviewed papers were selected for consideration based on relevance. Two independent researchers reviewed the title, abstracts, and papers that did not meet the criteria for inclusion in the review were excluded through discussion. Two independently working researchers analyzed the results obtained to avoid errors. Any inconsistencies were resolved through discussion. Exclusion criteria: reviews, research notes, book chapters, case studies, and grants. A total of 33 original studies, were selected for review (Table 1).

Table 1. Description of studies included in the systematic review.

First Author	Year	Source	References
Yu et al.	2003	Scopus, WoS	(C. Yu et al., 2003)
Laitinen et al.	2004	Scopus, WoS	(Laitinen et al., 2004)
Greenblatt et al.	2006	Cohrane, Ebsco, PubMed, Scopus, WoS	(Greenblatt et al., 2006)
Grenier et al.	2006	Cohrane, Ebsco, PubMed, Scopus	(Grenier et al., 2006)
Z. Li et al.	2006	Cohrane, Ebsco, PubMed, Scopus	(Z. Li et al., 2006)
Lilja et al.	2007	Scopus, WoS	(Lilja et al., 2007)
Iwao et al.	2008	Scopus	(IWAO et al., 2008)
Gotteland et al.	2008	PubMed	(Gotteland et al., 2008)
Mohammed Abdul et al.	2008	Cohrane, Ebsco, Embase, PubMed, Scopus, WoS	(Mohammed Abdul et al., 2008)
Ushijima et al.	2008	Cohrane, Ebsco, Scopus	(Ushijima et al., 2009)
M. Li et al.	2009	Ebsco, Scopus	(M. Li et al., 2009)
Ansell et al.	2009	Cohrane, Ebsco, Embase, PubMed, Scopus, WoS	(Ansell et al., 2009)
Ngo et al.	2009	Scopus	(Ngo et al., 2009)
Uesawa and Mohri	2010	Ebsco, Embase, Scopus, WoS	(Uesawa & Mohri, 2010)
Mellen et al.	2010	Ebsco, Scopus,	(Mellen et al., 2010)
Kim et al.	2011	Ebsco, PubMed, Scopus	(Kim et al., 2011)
Wanwimolruk et al.	2012	Ebsco, Embase, Scopus	(Wanwimolruk et al., 2012)
Diarra et al.	2013	Embase	(Diarra et al., 2013)
Hanley et al.	2013	Cohrane, Ebsco, Embase, PubMed, Scopus, WoS	(Hanley et al., 2013)
Langhammer and Nilsen	2014	Ebsco, Embase, Scopus, WoS	(Langhammer & Nilsen, 2014)
Choi et al.	2014	Ebsco, Embase, Scopus, WoS	(Choi et al., 2014)
Blanton et al.	2015	Scopus	(Blanton et al., 2015)
Zhong et al.	2015	Cohrane	(Zhong et al., 2015)
Shailender et al.	2017	Scopus	(Shailender et al., 2017)
Al-Juhaishi et al.	2018	Cohrane, Scopus	(Al-Juhaishi et al., 2018)
Sabarathinam and Vijayakumar,	2020	Scopus	(Sabarathinam & Vijayakumar, 2020)
Almomen et al.	2020	WoS	(Almomen et al., 2020)
Loretz et al.	2020	Embase, Scopus, WoS	(Loretz et al., 2020)
C. P. Yu et al.	2021	Ebsco, Scopus	(C.-P. Yu et al., 2021)
Arango-Varela et al.	2021	Scopus	(Arango-Varela et al., 2021)
Morita et al.	2022	Ebsco, Embase, Scopus, WoS	(Morita et al., 2022)
Husain et al.	2023	Scopus	(Husain et al., 2023)
Shibata et al.	2023	Scopus	(Shibata et al., 2023)

RESULTS & DISCUSSION

Table 2. Summary of the evidence for *Vaccinium*-drug interactions

Oral agents against blood clots – Warfarin

CRANBERRY JUICE DOSE	STUDY DESIGN	INR	RESULT
250 ml once daily for 7 days	7 patients with atrial fibrillation; constant warfarin dose for 3 months	2.28±0.54 for the cranberry group 2.13±0.50 for the placebo group	No clinically significant interaction
240 ml once daily for 2 weeks	30 patients on stable anticoagulant warfarin therapy	Minimally increased INR (range 3.38–4.52)	No clinically significant interaction
240 ml twice daily for 1 week	10 male patients on a stable warfarin dose	2.3 – 3.3	No clinically significant interaction
Concentrated cranberry juice GNC (3 capsules daily)	12 healthy males with known CYP2C9 and VKORC1 genotypes	2.5 – 3.1	Cranberry significantly increased the INR area under the curve by 30% in VKORC1 variant carriers (CT and TT alleles)
Cranberry juice orally (5 g/kg)	Female Sprague-Dawley rats weighing 300–450 g	10 hours after warfarin administration, INR value increased to 2.7 ± 0.5 after 24 hours	Cranberry 0.5 hours before warfarin significantly reduced overall systemic exposure to warfarin. Cranberry 10 hours post-warfarin significantly inhibited the elimination of S-warfarin, and the anticoagulant effect of warfarin was significantly enhanced.

Antibiotic Beta-lactams

ANTIBIOTIC	DOSE	STUDY DESIGN	RESULT
Amoxicillin and Cefaclor	4-fold single oral dose of amoxicillin 500 mg and 2 g + 250 ml of cranberry cocktail 500 mg of cefaclor + 350 ml of cranberry cocktail	8 healthy women	No clinically significant interaction confirmed. However, delayed absorption of amoxicillin and cefaclor was observed.
Chloramphenicol, oxacillin, amoxicillin, norfloxacin, rifampicin, vancomycin	Nutricran®90 (NC90), Decas Botanical Synergies (Wareham, MA, USA) Cranberry fraction FC111	Four strains of S. aureus grown in broth	Cranberry fraction FC111 affects PG synthesis of S. aureus and acts synergistically with β-lactam antibiotics.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

MEDICATION	CRANBERRY JUICE DOSE	STUDY DESIGN	RESULT
Diclofenac	The patient took 180 ml of cranberry juice twice a day for the first 5 days. On day 6, he was given one 25 mg tablet of diclofenac along with 180 ml of cranberry juice.	Eight healthy volunteers, male (n = 6) and female (n = 2), with an average age of 30.5 years	Cranberry juice inhibited CYP2C9 activity in vitro, but did not alter the pharmacokinetics of drugs metabolized by CYP2C9 in clinical situations.
Flurbiprofen	Berry juice (300 ml). 100 mg of flurbiprofen.	Healthy volunteers aged 19 to 54 years.	Berry juice has no effect on the AUC of flurbiprofen. Studies do not provide evidence for concerns regarding clinically significant pharmacokinetic interactions between cranberry juice and drugs that are substrates metabolized by CYP3A or CYP2C9.

Tumor necrosis factor (TNF) inhibitor

MEDICATION	CRANBERRY JUICE DOSE	STUDY DESIGN	RESULT
Etanercept	Matched etanercept and 50 ml of berry juice daily for 6 months.	Two hundred and one patients with systemic juvenile idiopathic arthritis (sJIA).	Symptoms and side effects were significantly reduced or did not occur. Berries lowered the levels of IL-1 alpha and beta and increased the levels of IL-1RA. Therefore, the combination therapy of blueberry and etanercept may reduce the severity of systemic juvenile idiopathic arthritis (sJIA) and should be developed as a new treatment method for sJIA.

CONCLUSION

The consumption of cranberry juice on a daily basis does not exhibit a significant interaction with warfarin; however, it is imperative to closely monitor the International Normalized Ratio (INR) in patients. Furthermore, cranberry juice has been shown to have no impact on the pharmacokinetics of drugs metabolized by CYP2C9 in clinical settings. Additionally, cranberries influence the synthesis of prostaglandins in Staphylococcus aureus and demonstrate a synergistic effect when used in conjunction with β-lactam antibiotics.

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