

# Exploring the evidence base on *Vitis vinifera* toxicity in dogs after ingestion - clinical effects, treatments, and management practices: A scoping review protocol.

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## ABSTRACT

### Structured summary

Evidence based veterinary medicine involves using the most up to date critically appraised evidence to supplement clinical decision making. The published literature on the topic of *Vitis vinifera* fruit (VVF) toxicosis in dogs could contain undiscovered knowledge that could be important for informing the clinical approach regarding these cases. A scoping review could map out what research has currently been performed, illuminating well described evidence and highlighting gaps that may warrant further research.

The databases interrogated will be CAB Abstracts, Medline, Embase, and Scopus. Data charted will include, *Vitis vinifera* products consumed, clinical effects shown due to intoxication, and treatments given.

## INTRODUCTION

### A background on *Vitis vinifera* fruit (VVF) toxicity in dogs

Multiple varieties of VVF have been reported as toxic in dogs. This includes grapes (Yoon et al., 2011), dried grapes (currants, raisins) (Stanley and Langston, 2008, Penny et al., 2003) and processed grape products such as grape marc (Schweighauser et al., 2020). The toxic component of VVF is currently unknown; a few hypotheses include possible contamination of the grape with heavy metals, pesticides, or other toxins (mycotoxins, ochratoxins), or an intrinsic component of the grape itself (e.g. Vitamin D excess; Gwaltney-Brant et al., 2001). Studies screening for such contaminants have been unable to find evidence of heavy metal or mycotoxin contamination (Gwaltney-Brant et al., 2001, Eubig et al., 2005). Recently, a case series studying similarities between cream of

tartar, tamarind and grape toxicities concluded that tartaric acid (an organic acid found naturally at a relatively high concentration in grapes) could be a possible interlinking factor between the three (Wegenast et al., 2022).

Clinical signs associated with VVF toxicity are varied but can include: gastrointestinal signs such as vomiting and diarrhoea; neurological signs such as ataxia; and cardiovascular signs such as bradycardia or tachycardia (Bates, 2021). Acute kidney injury (AKI) is a clinical sign of particular interest in cases of VVF toxicity due to mortality associated with organ damage. Similar to the nature of the toxic component, the toxic mechanism of renal tubular cell death remains currently undefined. Histopathology of the kidneys of VVF toxicity patients has shown necrosis of the proximal convoluted tubules with signs of regeneration (Mazzaferro et al., 2004); this is similar to findings in patients of tartaric acid toxicity although the toxic mechanism of tartaric acid is also unknown (Wegenast et al., 2022).

Due to the variable toxic dose rate, treatment guidance has recommended that consumption of any quantity of VVF warrants aggressive treatment which includes induction of emesis, administration of activated charcoal, aggressive fluid therapy for 48 hours, along with monitoring via biochemical analysis for 72 hours (Bates, 2021).

## Rationale

The concept of evidence-based medicine (EBM) (Guyatt et al., 1992), of which evidence based veterinary medicine (EBVM) is modelled (Doig, 2003), focuses on the “examination of evidence from clinical research” over “intuition, unsystematic clinical experience and pathophysiologic rationale” in clinical decision making. Evidence based veterinary medicine can be considered an iterative process, using the best available evidence to form a conclusion, updating and re-evaluating the outcome as new sources of evidence emerge, alongside incorporating owner, patient and veterinary factors in any considerations. Being able to use evidence in clinical decision making is reliant on having good quality evidence to use.

Unfortunately, much of the important information regarding VVF toxicity (such as dose rates or toxic mechanism) is currently unknown (Bates, 2021), which creates large gaps in knowledge around VVF toxicity, and has serious implications for clinicians wanting to use an EBVM approach. A scoping review could provide support to anyone treating canine VVF ingestion, by shedding light on the extent of evidence published and the context/power of the evidence published. This will also create a clear view of what evidence gaps exist.

As far as the authors are aware, there has not yet been a full scoping review conducted on the topic of VVF toxicity in dogs. The authors have screened the relevant evidence syntheses’ and associated databases of SYREAF (<https://syreaf.org/protocols/>), OSF (<https://osf.io/registries>), and VetSRev (<https://vetsrev.nottingham.ac.uk/>), along with the four literature databases to be used for this scoping review (CAB Abstracts, Medline, Embase, and Scopus).

## Objectives

The aim of this scoping review is to explore the evidence that has been reported regarding *Vitis vinifera* fruit ingestion in dogs. To accomplish this, the aim has been split into three objectives, each focusing on possible clinically significant components. The objectives are as follows:

Objective 1: "To what degree does the evidence show the types of *Vitis vinifera* fruit ingestion leading to a clinical problem?"

Objective 2: "To what degree does the evidence show the clinical signs of toxicity due to *Vitis vinifera* fruit ingestion?"

Objective 3: "To what degree does the evidence show the treatment methods given to patients who have ingested *Vitis vinifera* fruit?"

## Keywords

AKI; Canine; Grape; Grape toxicity; Raisin toxicity

## METHODS

### Protocol and registration:

This scoping review will follow the conduct guidance from the JBI methodology for scoping reviews (Peters et al., 2020), and the PRISMA-ScR guidance on reporting of scoping reviews (Tricco et al., 2018). It will be available at SYREAF ([www.syreaf.org](http://www.syreaf.org)) and on the Centre for Evidence-based Veterinary Medicine website.

### Eligibility criteria

This scoping review will include all research-based papers, with no restriction on study type, publication date or location. Grey literature, (for example, non-peer reviewed conference abstracts,) will be included as long as the literature contains novel data. All non-English papers will be included if the abstract is in English. The paper must at least partially focus on the topic of VVF ingestion in dogs and the toxicological effects caused or the treatment of such cases.

To aid in the selection of relevant papers, the following definitions have been formulated regarding the criteria of the scoping review:

**Research-based papers** – defined as any publication that provides novel data, (i.e. primary sources), or novel analysis of data (i.e. systematic reviews). This excludes narrative reviews and opinion pieces that either collate novel data from other studies or contain no novel data.

**Toxicological effects** - defined as any clinical effect present in the dogs that may be due to ingestion of *Vitis vinifera* fruit.

**VVF** - defined as all fruit products from the *Vitis vinifera* plant, excluding processed fruit (e.g. grape extract). This limitation has been imposed due to the time and resource constraints of the project. This definition does include ingestion of foodstuffs that contain whole VVF e.g. mince pies, fruit buns.

**Dogs** - defined as any animal from the species *Canis familiaris*, this includes all breeds, ages, and health statuses, but excludes un-owned dogs (e.g. wild or feral animals).

## Information sources

The following databases will be searched without date limits – CAB Abstracts, Medline, Embase, and Scopus. The papers found will be saved and filtered for relevance as detailed below. Once the information sources have been identified and filtered, backwards citation chaining of the relevant sources will be performed to ensure maximum saturation of all relevant sources.

## Search

Preliminary searches (see Appendix) were developed based upon search terms previously used by two of the authors (**Table 1 Search terms from previous project.**) These search terms were then broadened to suit the broader research question.

To include all possible information regarding whole VVF ingestion, efforts were made to compose a comprehensive list of foodstuffs containing whole VVF for inclusion within the search terms. This consisted of a keyword search of relevant papers found using the search terms from **Table 1** Search terms from previous project on the CAB Abstracts and Medline databases. A manual search of food encyclopaedias and cooking encyclopaedias located at the University of Nottingham's library ([NUsearch \(nottingham.ac.uk\)](http://NUsearch.nottingham.ac.uk)) was also conducted. It is acknowledged by the authors that the foodstuff search terms used for the scoping review may not necessarily be exhaustive and is likely to have an Anglocentric skew. When creating the search strategy, the help of an experienced academic librarian was enlisted (AA).

## Selection of sources of evidence

All databases will be searched on the same day, search results transferred to Endnote Online™ (The EndNote Team, Philadelphia, PA) and duplicates removed. For the evidence filtering process, the results will be imported into Rayyan (Mourad et al., 2016) which will be used to assist the screening of the papers, a manual deduplication will also occur at this stage. A flowchart will be utilised to screen the citations for eligibility, first filtering the abstract and title followed by a full text screening. This flowchart will first be tested via a piloting exercise. This will serve to ensure consistency between reviewers as well as show any refinements that may need to be made to the evidence filtering flowchart. Once any adjustments have been made to the screening methodology, the rest of the papers will be screened. Screening on title and abstract, and then the full text, will be undertaken by 2 independent reviewers.

### Title and abstract review -

1 – Is the title and abstract in **English**?

- Yes/maybe – continue to question 2
- No – exclude study

2 – Is the study about **dogs** eating **VVF** (including VVF extract)?

- Yes/maybe – continue to question 3
- No – exclude study

3 – Does the study at least partially focus on **the clinical signs of intoxication or treatment** of dogs that have ingested VVF?

- Yes/maybe – continue to question 4
- No – exclude study

4 – Is the study on **owned, domesticated** dogs?

- Yes/maybe – continue to question 5
- No – exclude study

5 – Is the study about **unprocessed VVF**?

- Yes/maybe – continue to question 6
- No – exclude study

6 – Does the study contain **novel** data?

- Yes/maybe – include study for whole text filtering
- No – exclude study

#### Full text review:

1 – Is it possible to gain access to the entire source via the University of Nottingham library or British library services?

- Yes – continue to question 2
- No – exclude study

2 – Is the study about dogs **eating** VVF (excluding those relating to VVF extract)?

- Yes – continue to question 3
- No – exclude study

3 – Does the study at least partially focus on **the clinical signs of intoxication or treatment** of dogs that have ingested VVF?

- Yes – continue to question 4
- No – exclude study

4 – Is the study on **owned, domesticated** dogs?

- Yes – continue to question 5
- No – exclude study

5 – Is the study about **unprocessed VVF**?

- Yes – continue to question 6
- No – exclude study

6 – Does the study contain **novel** data?

- Yes – include study
- No – exclude study

#### Data charting process

To chart the data, a Microsoft Form will be used to capture the information which will then be exported into a Microsoft Excel document. Similar to the screening process, a

piloting exercise will be conducted with all reviewers to ensure consistency across reviewers as well as ensuring no refinements need to be made regarding the form. Two reviewers will undertake the charting of each paper independently. Disagreements between assessors will be attempted to be resolved via discussion; a third reviewer will be consulted if agreement between the two reviewers cannot be reached.

## Data items

An example of the data charting items present on the form is as follows:

Title of study,

Author,

Date of publish,

### **Study descriptors,**

Location of study,

Source of data for the study,

Type of study,

Aims of study,

### **Patient descriptors,**

Number of patients,

### **Vitis vinifera fruit products consumed,**

Type of fruit consumed (fresh, dried, fruit cake),

Quantity of VVF consumed,

### **The clinical signs of intoxication shown,**

Definition of AKI,

Number of patients with clinical signs,

List of symptoms categorised into body systems,

### **Treatment,**

Treatments given,

Duration of treatments,

### **Study outcomes,**

Outcome of patients,

## Critical appraisal

A critical appraisal process will not be undertaken for this scoping review.

## Synthesis of results

Results will be expressed in a tabulated and diagrammatic form with supplementary descriptive text. The data charted will be used to answer the three objectives discussed earlier in the protocol.

## Funding

University of Nottingham. The funders had no involvement in the development of the protocol or the study design of the scoping review.

## Appendix

*Table 1 Search terms from previous project*

<b>Components</b>	<b>Dogs</b>	<b>Toxicity</b>	<b>Vitis vinifera fruit ingestion</b>
<b>Keywords</b>	dog, dogs, canine, canines, canis, canid, canids, canidae	poison, poisons, poisoned, poisoning, toxicity, toxicities, toxicosis, intoxication, intoxicating, intoxicated, toxic substances, plant poisoning, GRT	grape, grapes, vitis, vitis vinifera, raisin, raisins, sultana, sultanas, currant, currants
<b>Subject headings, Medical subject headings (MeSH), thesaurus terms</b>	dogs, canidae, canis	toxic substances, poisoning, toxicity	grapes, vitis, vitis vinifera, raisins, sultanas

Table 2 CAB Abstracts

Components	Dog	Vitis vinifera fruit
<b>Keywords</b>	dog, dogs, canine*, canines, canis, canid*	grape*, vitis, vitis vinifera, raisin*, sultana*, currant*,  dried Fruit*, christmas cake*, fruit cake*, mince pie*, fruit loaf, strudel*, fruit bun*, currant bun*, hot cross bun*, bertolina, panettone, eccles cake*, stollen*, spotted dick, Malt loaf*, scone*, snack bar*
<b>Subject headings, Medical subject headings (MeSH), thesaurus terms</b>	dogs, canis, canidae	grapes, vitis, vitis vinifera, raisins, sultanas, dried fruit

Table 3 Medline

Components	Dog	Vitis vinifera fruit
<b>Keywords</b>	dog, dogs, canine*, canines, canis, canid*	grape*, vitis, vitis vinifera, raisin*, sultana*, currant*,  dried Fruit*, christmas cake*, fruit cake*, mince pie*, fruit loaf, strudel*, fruit bun*, currant bun*, hot cross bun*, bertolina, panettone, eccles cake*, stollen*, spotted dick, Malt loaf*, scone*, snack bar*
<b>Subject headings, Medical subject headings (MeSH), thesaurus terms</b>	dogs, canidae	vitis



Table 4 Embase

Components	Dog	Vitis vinifera fruit
<b>Keywords</b>	dog, dogs, canine*, canines, canis, canid*	grape*, vitis, vitis vinifera, raisin*, sultana*, currant*,  dried Fruit*, christmas cake*, fruit cake*, mince pie*, fruit loaf, strudel*, fruit bun*, currant bun*, hot cross bun*, bertolina, panettone, eccles cake*, stollen*, spotted dick, Malt loaf*, scone*, snack bar*
<b>Subject headings, Medical subject headings (MeSH), thesaurus terms</b>	dog, canis, canidae	grape, vitis

Table 5 Scopus

Components	Dog	Vitis vinifera fruit
<b>Keywords</b>	dog, dogs, canine*, canines, canis, canid*	grape*, vitis, vitis vinifera, raisin*, sultana*, currant*,  dried Fruit*, christmas cake*, fruit cake*, mince pie*, fruit loaf, strudel*, fruit bun*, currant bun*, hot cross bun*, bertolina, panettone, eccles cake*, stollen*, spotted dick, Malt loaf*, scone*, snack bar*

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