

# Co-ingestion of herbal medicines and warfarin

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## SUMMARY

**Background:** A large proportion of patients use herbal remedies with a potential to interact with prescribed drugs. Such interactions can be dangerous, particularly if the therapeutic window of the prescribed drug is small, as with warfarin.

**Aims:** Our aim was to estimate the prevalence of the use of herbal medicines by patients taking warfarin (co-ingestion).

**Design of study:** Postal questionnaire.

**Setting:** General practices in the South West of England.

**Method:** Thirty-five general practices in Devon and Somerset identified 2600 patients taking warfarin and sent postal questionnaires to them.

**Results:** One thousand, three hundred and sixty usable responses were received (response rate = 54.2%). One or more of the specified herbal remedies thought to interact with warfarin were taken by 8.8% of all patients. Complementary or homeopathic treatments not specified in the survey questionnaire were taken by 14.3% of responders. Overall, 19.2% of responders were taking one or more such medicines. The use of herbal medicines had not been discussed with a conventional healthcare professional by 92.2% of patients. Twenty-eight point three per cent of responders thought that herbal medicines might or definitely could interfere with other drugs prescribed by their doctor, however, patients taking any non-prescribed medication were less likely to believe this ( $\chi^2 = 20$ , degrees of freedom = 1,  $P < 0.001$ ).

**Conclusion:** A substantial proportion of patients taking warfarin in southwest England self-medicate with both herbal medicines that are thought to interact with warfarin and with others of unknown effect, usually without informing their healthcare team. Patients have a responsibility to mention such non-prescribed medication to their general practitioners, and general practitioners also have a responsibility to ask whether such co-ingestion is occurring.

**Keywords:** alternative medicine; complementary medicine; complementary therapies; drug interactions; herb-drug interactions; self-medication; warfarin.

## Introduction

COMPLEMENTARY or alternative medicine, and specifically herbal remedies, have grown in popularity. The usage of herbal medicines by the general population of the United States (US), for instance, increased by 380% between 1990 and 1997.<sup>1</sup> In the United Kingdom (UK), herbal medicine is the most popular branch of complementary medicine.<sup>2</sup> According to these and other survey data, medical herbalism was most commonly employed for allergies, insomnia, respiratory problems, and digestive problems.<sup>3</sup>

The notion that herbal medicines are natural and therefore safe is as widespread as it is misleading. Some of these remedies have been associated with severe adverse effects caused by the toxicity of the herbal ingredients.<sup>4</sup> Others may cause problems because of contamination or adulteration.<sup>5</sup> The most significant risk associated with herbal medicines, however, is that of herb-drug interactions. Despite the fact that this area is still grossly under-researched, the list of herbal medicines with a potential to interact with synthetic drugs is long.<sup>6,7</sup> Herb-drug interactions are particularly important if the therapeutic window of the synthetic medicine is small. Warfarin is an example of such an agent. As it is a commonly used drug, interactions between herbal medicines and warfarin are of particular relevance (Table 1).<sup>8</sup> Given this background, we wanted to further explore the extent to which patients are taking both herbal medicines and warfarin (co-ingestion).

## Method

All practices within the Somerset and North and East Devon Primary Care Research Network area were invited by letter to participate. Each participating practice was paid between £50 and £200, depending on their size, to cover their administrative costs. Approval was obtained from the Ethics Committees of West Somerset, East Somerset and Exeter.

It is normal practice in southwest England for most patients on warfarin to be monitored by their general practitioner (GP). Regular international normalised ratio (INR) tests are carried out and GPs advise on any dose change. Only a small minority of patients attend hospital anticoagulation clinics.

A questionnaire was designed to document the co-ingestion of warfarin and complementary medicines (Supplementary appendix 1). The main target was a specific group of herbal compounds that had previously been implicated for interacting with warfarin: garlic, ginseng, ginkgo biloba, feverfew, ginger, and St John's wort (Table 1).<sup>8</sup> A small pilot study was undertaken in one Somerset general practice to assess and optimise its level of patient acceptability. The pilot questionnaire was sent to 25 patients. Their responses were excluded from the main analysis and some minor modifications were made to the custom-made questionnaire.

Participating practices undertook a search of their computerised records for all patients who were taking warfarin,

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**HOW THIS FITS IN***What do we know?*

Complementary or alternative medicines are increasingly used by the population and are not recorded by practice-based prescribing systems. Many of these medicines can interact with warfarin, which is also increasingly prescribed for a range of medical conditions, especially in the elderly.

*What does this paper add?*

One out of five patients prescribed warfarin were taking one or more complementary medicines. Most were uncertain about whether such co-ingestion was important. Those taking complementary medicines were less likely to believe that it was important. GPs and patients both have responsibilities to share such information about co-ingestion to reduce potential harm.

and sent out the questionnaire, a covering letter, and a freepost return envelope to all such patients. Two weeks later, they sent out a short reminder letter to the same group of patients. Replies were returned to the central research office and were anonymous, unless the patient chose to write contact details on the returned questionnaire.

Useable replies were entered onto a database and SPSS was used for analysis. Data were analysed using descriptive statistics. Where appropriate, any relation between patients' beliefs about herb-drug interactions were analysed by the length of time they had been on treatment, the reason for taking treatment, their sex, and whether they took any herbal medicines. Non-parametric comparisons were done using the Mann-Whitney statistic or Spearman's correlation coefficient.

**Results**

Out of the 159 practices in Somerset and Devon, 35 agreed to participate, and they sent out a total of 2600 questionnaire packs to patients. Of these, 84 patients contacted the research office to say they were no longer taking warfarin, and five relatives telephoned to say that the index patient had died. Thirty-eight questionnaires were returned uncompleted and 80 patients contacted the research office to decline to take part. Useable replies were thus received from 1360 patients (corrected response rate = 1360/2511 [54.2%]). Of 1360 responders, 849 (63.1%) were men and 497 (36.9%) were women (14 missing values). Of these, 40 (3%) had been taking warfarin for less than 3 months, 117 (8.7%) for 3–6 months, 112 (8.3%) for 7–12 months, and the majority, 1079 (80.0%), for longer than 12 months (12 missing values). The reasons given for taking warfarin are summarised in Table 2.

Overall, 261/1360 (19.2%) patients reported taking one or

more complementary medicines in this survey. Of these, 119 (8.8%) responders reported taking one or more of the herbal medications specified on the questionnaire and thought to interact with warfarin. Non-responders may be less likely to be taking such preparations, and if none of them were, the prevalence could be as low as 4.7%. Of the 119 taking herbal medicines, 3 (2.5%) reported adverse events; this amounts to 0.12% of the total sample: 99/1355 (7.3%) patients were taking garlic, 66 on a daily basis; 13 (1.0%) were taking ginseng; 20 (1.5%) ginkgo biloba; 2 (0.2%) feverfew; 12 (0.9%) ginger; and 6 (0.5%) St John's wort. One hundred and ninety-four (14.3%) patients were taking other herbal, complementary, or homeopathic treatments, not specified in the survey questionnaire.

Responders were asked if they thought that the herbal medicine could interfere with other drugs prescribed by their doctor. Of 1109 answering this question (251 missing values) 56 (5%) definitely felt that they could, 258 (23.3%) thought they might, 582 (52.5%) were uncertain, 168 (15.1%) thought probably not, and 45 (4.1%) definitely not. Patients taking herbal preparations were asked if they had discussed their herbal remedy use with any professionals. Fifty-six (4.1%) of 1353 had discussed it with their GP, 21 (1.6%) with their practice nurse, 14 (1.0%) with a hospital consultant, 5 (0.4%) with a hospital nurse, and 10 (0.7%) with a pharmacist or chemist. It follows that 92.2% of these patients had not discussed their use of herbal medicines with a conventional healthcare professional. A further 16 (1.2%) had discussed it with other people; for example, a husband, wife, daughter, son or friend; or a herbalist, homeopath or an assistant in a health food shop.

Patients' beliefs were related to whether or not they were taking any additional complementary preparations. Patients taking any complementary medicine treatment were less likely to believe that herbal preparations could interfere with other medicines prescribed by their doctor; Mann-Whitney test,  $P < 0.001$ , for those taking complementary medicines, median score = 3 (interquartile range [IQR] = 2–4) versus median = 3 (IQR = 2–3) for those not currently taking complementary preparations. Similar results were found if the analysis was restricted to patients taking or not taking the six specified herbs known to interact with warfarin; Mann-Whitney test,  $P < 0.001$ , for those currently taking herbal preparations, median = 3 (IQR = 2–4) compared with median = 3 (IQR = 2–3) for those not taking them. Their belief was not related to the reason for taking warfarin, their sex nor to the length of time of warfarin medication.

**Discussion**

Our results suggest that a considerable proportion of patients

Table 1. Data about specific herbal medicines thought to interact with warfarin.

Name (Latin)	Main indication	Efficacy demonstrated through rigorous trials	Potential interaction with warfarin
Garlic ( <i>Allium sativum</i> )	Hypercholesterolaemia	Yes <sup>15</sup>	Increased risk of bleeding
Ginseng ( <i>Panax ginseng</i> )	Various	No <sup>16</sup>	Increased risk of bleeding
Ginkgo biloba ( <i>Ginkgo biloba</i> )	Dementia	Yes <sup>17</sup>	Increased risk of bleeding
	Intermittent claudication	Yes <sup>18</sup>	
Feverfew ( <i>Tanacetum parthenium</i> )	Migraine prevention	Yes <sup>19</sup>	Increased risk of bleeding
Ginger ( <i>Kaempferia galanga</i> )	Nausea/vomiting	Yes <sup>20</sup>	Increased risk of bleeding
St John's wort ( <i>Hypericum perforatum</i> )	Mild to moderate depression	Yes <sup>21</sup>	Increased risk of clotting

Table 2. Reasons stated by responders for taking warfarin.<sup>a</sup>

Reason	Number (%)
Irregular heartbeat	326 (24.5)
Atrial fibrillation	162 (12.2)
Heart valve replacement	174 (13.1)
Deep vein thrombosis	174 (13.1)
Pulmonary embolism	132 (9.9)
Heart failure	89 (6.7)
Stroke	136 (10.2)
To thin the blood	85 (6.4)
Not sure	45 (3.4)
Unspecified clotting problem	9 (0.7)

<sup>a</sup>n = 1332, missing values = 28.

who take warfarin also self-medicate with herbal remedies. The vast majority do not discuss this with their doctor or other healthcare professionals. Several of the remedies that patients self-prescribe have the potential to interact with warfarin and alter their INR (Table 1).<sup>9</sup> Because patients do not usually raise the subject of co-ingestion with their professional advisers, they are putting themselves at increased risk of side effects such as bleeding. Several reports have been published of incidences in which patients on warfarin have suffered serious harm through herb-warfarin interactions.<sup>8</sup> In our opinion, GPs prescribing warfarin should always ask about these potential interactions because of the widespread and growing use of herbal medicines.

Our survey focused on herbal interactions with warfarin. However, the risks of herbal remedies are not confined to this particular situation. Virtually all herbal medicines are associated with some degree of toxicity owing to pharmacologically active herbal ingredients.<sup>10-13</sup> Because the herbal medicine sector is under-regulated (herbal remedies are not normally marketed as medicines but as dietary supplements), the quality of some herbal preparations is suboptimal. In particular, there are concerns about contamination, adulteration, and misidentification.<sup>4</sup>

The message that seems to emerge is that both doctors and their patients have a joint responsibility to raise the issue of possible or actual herbal medicine use in general, and herb-drug interactions in particular, when warfarin is prescribed. Recently, several books that are well-suited for this purpose have become available.<sup>10-13</sup>

Since herbal remedies are popular, and most indicators predict future growth of this sector, doctors need to reconsider their general attitude towards this subject. GPs should actively ask patients what form of complementary medicine they are using. Once it has been clarified that a patient uses herbal treatments, it is counter-productive to be dismissive about this topic. Non-judgmental and unbiased information would be more helpful for the patient and less likely to alienate patients from their GP.<sup>14</sup> To give such advice would obviously require GPs to know about herbal medicines. Doctors 'must tread a line between an apparently sympathetic stance that might be interpreted as an endorsement for unproven therapies and categorical disapproval, which would discourage patients from revealing their use of herbal remedies'.<sup>4</sup> To pro-

vide informed advice, the evidence base needs improving. We would strongly suggest further primary care-based research to explore whether co-ingestion of herbal remedies and warfarin definitely causes problems with INR control and/or with side effects such as bleeding. At present it is unknown how frequently co-ingestion causes clinical problems.

Our survey has several significant limitations. It was conducted locally and yielded a suboptimal response rate. We therefore cannot be certain that the results are representative of the UK as a whole. The questionnaires were custom made for our purposes, thus their validity could be questioned. Considering these limitations, our findings should be interpreted with caution.

In conclusion, many patients in southwest England take herbal remedies in addition to warfarin without telling their healthcare team about it. Herb-warfarin interactions could put patients at risk. GPs need to be better informed and patients need to disclose more regularly about any herbal or other complementary medicine co-ingested with warfarin.

## References

1. Eisenberg DM, Davis RB, Ettner SL, *et al.* Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998; **280**: 1569-1575.
2. Ernst E, White AR. The BBC survey of complementary medicine use in the UK. *Complement Ther Med* 2000; **8**: 32-36.
3. Ernst E. Herbal medicines put into context. *BMJ* 2003; **327**: 881-882.
4. De Smet PAGM. Herbal remedies. *N Engl J Med* 2002; **347**: 2046-2056.
5. Ernst E. Toxic heavy metals and undeclared drugs in Asian herbal medicines. *Trends Pharmacol Sci* 2002; **23**: 136-139.
6. Ernst E. Possible interactions between synthetic and herbal medicinal products. Part 1: a systematic review of the indirect evidence. *Perfusion* 2000; **13**: 4-6, 8-15.
7. Ernst E. Interactions between synthetic and herbal medicinal products. Part 2: a systematic review of the direct evidence. *Perfusion* 2000; **13**: 60-70.
8. Gundling K, Ernst E. Herbal medicines: influences on blood coagulation. *Perfusion* 2001; **14**: 336-342.
9. Harkness R, Bratman S. *Handbook of drug-herb and drug-supplement interactions*. St Louis: Mosby, 2003.
10. Ernst E, Pittler MH, Stevinson C, *et al.* *The desktop guide to complementary and alternative medicine*. Edinburgh: Mosby, 2001.
11. Schulz V, H  nsel R, Tyler VE. *Rational phytotherapy. A physician's guide to herbal medicine*. 4th edn. Berlin: Springer-Verlag, 2001.
12. McKenna DJ, Jones K, Hughes K. *The desk reference for major herbal supplements*. New York: Haworth Press, 2002.
13. Fugh-Berman A. *The 5-minute herbal and dietary supplement consult*. Philadelphia: Lippincott, Williams and Wilkins, 2003.
14. Eisenberg DM. Advising patients who seek alternative medical therapies. *Ann Intern Med* 1997; **127**: 61-69.
15. Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia. A meta-analysis of randomised clinical trials. *Ann Intern Med* 2000; **133**: 420-429.
16. Vogler BK, Pittler MH, Ernst E. The efficacy of ginseng. A systematic review of randomised clinical trials. *Eur J Clin Pharmacol* 1999; **55**: 567-575.
17. Ernst E, Pittler MH. Ginkgo biloba for dementia: a systematic review of double-blind placebo-controlled trials. *Clin Drug Invest* 1999; **17**: 301-308.
18. Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of intermittent claudication. A meta-analysis. *Am J Med* 2000; **108**: 276-281.
19. Vogler BK, Pittler MH, Ernst E. Feverfew as a preventive treatment for migraine: a systematic review. *Cephalalgia* 1998; **18**: 704-708.
20. Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. *Br J Anaesth* 2000; **84**: 367-371.
21. Linde K, Ramirez G, Mulrow CD, *et al.* St John's wort for depression — an overview and meta-analysis of randomised clinical trials. *BMJ* 1996; **313**: 253-258.

## Supplementary information

Additional information accompanies this paper at: <http://www.rcgp.org.uk/journal/index.asp>

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