Interactions of herbal products and issues to consider in the treatment of diabetes

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In this article, the *Stockley's Herbal Medicines Interactions* and *Herbal Medicines* editorial teams provide an overview of herbal products and their potential to interact with conventional medicines. They also discuss the use of herbal products in people with diabetes.

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It is known that the use of herbal products is increasing dramatically, especially in Europe, the US and Australasia; however, it is difficult to precisely measure the extent of herbal product use in a largely unregulated market. In the US, annual retail sales of herbal products were estimated to be $4.2 billion (approximately equivalent to £2.8 billion*) in 2000 and over $5.2 billion (£3.4 billion*) in 2011, with sales steadily increasing every year since 2004 (Qato et al, 2008). In the UK, retail sales of herbal products are reported to have increased by 43% in the period from 1994 to 1998, with retail sales of licensed herbal products reported to be £50 million in 1998 (Williamson et al, 2013).

Despite the ease of access to, and widespread purchasing of, herbal products, their use is not without concern. This is chiefly because the pharmacological properties and potential interactions of herbal products are often less well understood than those of conventional medicines, increasing the risk of adverse effects and drug interactions. This article will explore the issues that surround the safety of such products, placing a particular emphasis on concerns resulting from drug interactions, and with a focus on diabetes.

What are the issues surrounding the use of herbal products?

Published evidence

The increasing use of herbal products by the general public presents several challenges to healthcare professionals, including the ability to provide evidence-based advice to patients on the use, indications, interactions and safety profile of herbal products, since good-quality data are often lacking. This lack of good-quality, evidence-based data can be attributed to several factors.

One such factor is that the regulatory process for conducting human clinical trials into the safety and efficacy of herbal products is time-consuming and expensive. The naturally occurring state of herbal medicines also means that there is little chance of a patent application being successful, and so there is little financial incentive for manufacturers to invest in research. As a result, there are relatively few clinical studies when viewed against the large array of herbal products on the market. The vast majority of the available data come from either isolated case reports or *in vitro* and animal studies, which, although useful in guiding the direction of future research, do not in themselves necessarily extrapolate to the clinical situation.

Another reason for the paucity of good-quality clinical data is that many herbal products have been used traditionally for years with relatively few cases of adverse effects or interactions coming to light, something which can often be the trigger for formalised research. However, many adverse reactions or interactions go unreported, even with conventional medicines, and this is likely to be further exacerbated with herbal products, as many patients consider herbal products to be natural and therefore "safe". Some patients also see no reason to disclose the use of any herbal products to their healthcare providers, perhaps through fear of disapproval but, equally, because they might not be asked for this

*Using an exchange rate taken at the time of writing.

Article points

1. Public health concerns regarding the quality and safety of herbal products include the potential adulteration of herbal products, inconsistent quality control on herbal constituents, and varying constituents in different parts of a herb.
2. All manufactured herbal medicines that can be shown to have been used traditionally for a number of years, reach a safety standard, are suitable for use without medical supervision, and are available in the UK must be registered under the Traditional Herbal medicine Registration scheme or have a marketing authorisation.
3. Some herbal products have the potential to affect blood glucose concentrations and interact with conventional antidiabetes drugs.
4. Healthcare professionals have a responsibility to educate people with diabetes that herbal products can carry the same risks as conventional medicines.

Key words

- Herbal medicines
- Interactions

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information. Furthermore, a lack of clinical reports of problems associated with the use of herbal products can also contribute to the assumption that these products are safe. Nevertheless, the possibility that many herbal products might, in fact, have a generally safe profile and do not interact to a clinically relevant extent with conventional medicines should not be discounted.

One further factor complicating research into herbal products is that any in-depth analysis is not straightforward because of the very nature of the material being studied – the variability of plant specimens and their related species, plant extracts, products, and even batches of the same product can make it difficult, and expensive, to isolate the specific pharmacologically active constituent involved in a particular interaction or adverse effect, and therefore difficult to establish exactly what the risks surrounding their use might be (MedicinesComplete, 2013).

Quality issues

Public health concerns regarding the quality and safety of commercially available herbal products include their potential adulteration with prohibited or contaminated substances, and differences between the labelled and actual contents of these products. For example, the trade of a species of Panax ginseng called *Panax quinquefolius* is restricted under conservation laws, and export from the US of the wild roots of *P. quinquefolius* is illegal until the roots are at least 10 years old and have four leaves (US Fish & Wildlife Service, 2005). However, these trade restrictions, and a boost in the demand for ginseng worldwide, increases the risk that *P. quinquefolius* could be adulterated, which might in turn exacerbate the risk of unexpected adverse effects.

In addition, some herbal products have been found to be contaminated with conventional drugs. For example, the US Food and Drug Administration has previously issued a warning that some herbal products which are claimed to be beneficial for diabetes were found to contain the antidiabetes drugs glibenclamide and phenformin. Contamination with phenformin is particularly worrying, as it was withdrawn from some countries following concerns about its toxicity (US Food and Drug Administration, 2013). In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has reported similar cases of adulteration of herbal products with glibenclamide, including Chinese herbal products sold for the treatment of erectile dysfunction (MHRA, 2008).

These safety and quality issues highlight the need to regulate herbal products and for healthcare professionals to have up-to-date scientific information on the quality, safety and efficacy of such products.

Regulation

Recognising the need for reliable clinical and safety data on the use of herbal products, the EU issued a directive in 2004 concerning

traditional herbal medicinal products (European Parliament, 2004); in response, the MHRA launched the Traditional Herbal medicine Registration (THR) scheme (see *Box 1*).

Under the THR scheme, currently unlicensed manufactured herbal medicines that have been used traditionally for a specific purpose over a number of years, and that reach a set safety standard, can officially be registered as a herbal medicine by the UK regulatory authorities. The MHRA restricts the use of the term "herbal medicine" to any herbal product that is sold claiming to contain active ingredients that will "correct or modify a physiological function in human beings" (MHRA, 2008). It is now mandatory for all manufactured preparations of herbal medicines available in the UK to either be registered under the THR scheme or hold a marketing authorisation (MA) as required for conventional medicines. As part of the THR procedure, a summary of product characteristics, similar to those required for licensed conventional drugs, must be written for each herbal medicine, based on safety data. As for conventional medicines, this includes sections on contraindications, precautions for use and interactions. The interactions data are often based on experimental evidence (MedicinesComplete, 2013); as discussed above, clinical data are often lacking.

The THR scheme ensures that herbal medicines available on the UK market meet certain safety standards. However, unlike with MAs, the THR scheme does not require evidence of efficacy. Herbal products that are sold without any written recommendation purporting to medical benefits are termed herbal remedies, and are exempt from the registration process (MedicinesComplete, 2013).

Box 1. Traditional herbal medicine registration.

- Since 30 April 2011, all manufactured herbal medicines available on the UK market that can be shown to have been used traditionally and that fulfil safety requirements require traditional herbal medicine registration (THR) or a marketing authorisation (MA).
- Products must reach specific safety and quality standards, and acceptable evidence of traditional use of the product must be presented.
- The herbal medicine must be suitable for use without medical supervision.
- Registered herbal medicines have a THR logo (see right) and number on the product label, and those with an MA have a product licence number.

Based on the Medicines and Healthcare Products Regulatory Agency's guidance on herbal medicines regulation (available at: http://bit.ly/14hmukf [accessed 18.07.13]).

Page points

1. Drug interactions can generally be divided into two different types: those that affect the metabolism of a drug (pharmacokinetic interactions) and those that lead to additive or antagonistic effects because of their pharmacological or physiological effects (pharmacodynamic interactions).
2. The available clinical evidence for interactions between herbal products and antidiabetes drugs is sparse, but it suggests that these interactions are commonly pharmacodynamic in nature.
3. In people with diabetes, the additive effects of a herbal product which has blood-glucose lowering effects might be beneficial; however, it might also put the individual at greater risk of hypoglycaemia.

Herbal product interactions with conventional antidiabetes drugs

In general, drug interactions can be divided into two different types: those that affect the metabolism of a drug (pharmacokinetic interactions) and those that lead to additive or antagonistic effects because of their pharmacological or physiological effects (pharmacodynamic interactions). Drug interactions between antidiabetes agents and other conventional medicines are commonly pharmacodynamic in nature: the blood glucose-lowering effects of the antidiabetes drug are increased or antagonised (Williamson et al, 2013). Similarly, some herbal products have been reported to affect blood glucose concentrations when taken alone and therefore might result in a pharmacodynamic interaction when taken with antidiabetes drugs. Examples of herbs that have been reported to affect blood glucose concentrations are listed in *Table 1*.

The available clinical evidence for interactions between herbal products and antidiabetes drugs is sparse, but it suggests that these interactions are also commonly pharmacodynamic in nature. Some examples are listed in *Table 2*.

Giving advice to patients on the use of herbal products with conventional drugs

In general, patients should be encouraged to recognise that, just because herbs are naturally occurring, this does not mean they are "safe" and will not potentially have pharmacological effects or interact with conventional drugs. In fact, the origin of many conventional medicines used today (such as digoxin and paclitaxel) can be traced back to plants.

In general, the decision on whether or not to recommend that a patient takes a particular herbal product would ideally be based on sound clinical evidence. However, as discussed above, this is often lacking. Therefore, any advice should be considered in light of the available evidence (clinical or experimental) and the severity of any reported interactions, and weighed against how essential it is for the patient to use the herbal product. The patient's underlying medical condition, how likely it is that this condition might be affected by the herbal product, and the likely outcome of this effect should also be considered.

In people with diabetes, the additive effects of a herbal product which has blood glucose-lowering effects might be beneficial; however, it might also put the individual at greater risk of hypoglycaemia. Equally, given the importance

Table 1. Examples of herbs and herbal products that have been reported to affect blood glucose concentrations (MedicinesComplete, 2013).

Hypoglycaemia	Hyperglycaemia
Agrimony	Elecampane
Asparagus	Ginseng, Panax
Burdock	Hydrocotyl
Damiana	Rosemary
Devil's Claw	
Elecampane	
Fenugreek	
Garlic	
Ginseng, Panax (*Panax ginseng*, Asian ginseng)	
Ginseng, Panax (*Panax quinquefolius*, American ginseng)	
Juniper	
Nettle	
Senega	

Table 2. Some examples of herbs and dietary supplements that have been reported to interact with antidiabetes drugs (Williamson et al, 2013).

Opposing effects	
Glucosamine	Unexpected increases in blood glucose concentrations have been reported in people with diabetes taking glucosamine sulphate or glucosamine with chondroitin. However, a controlled study found that glucosamine with chondroitin had no effect on glycaemic control in people taking oral antidiabetes drugs.
St John's wort	St John's wort slightly decreases the exposure to rosiglitazone (suspended in Europe) and gliclazide; its effects on pioglitazone are unclear. The pharmacokinetics of repaglinide and tolbutamide are unaffected by St John's wort.
Additive effects	
Karela	Karela can increase the blood glucose-lowering effects of chlorpropamide and other antidiabetes drugs.
Fenugreek	Fenugreek might have a modest antidiabetes effect when taken with sulphonylureas.
Aloe vera	Aloe vera juice reduces blood glucose concentrations in people with diabetes taking glibenclamide.

Herbal products and dietary supplements derived or prepared from a number of plants have been found to interact with antidiabetes drugs (from left to right: St John's wort, karela, fenugreek and aloe vera [see Table 2 *for more details]).*

of good blood glucose control in the prevention of the potential long-term complications of diabetes, such as retinopathy and kidney disease, consideration must be given to the likely outcome if a person with the condition takes a herbal medicine that might cause hyperglycaemia. With limited available clinical data, it can be difficult to make this judgement; engagement with people with diabetes is important to ensure that they are aware of all the possible treatment options in order to optimise the management of their condition.

It is also important to remember that patients do not respond uniformly. Genetic make-up, ethnic background, sex, renal and hepatic functions, nutritional state, age and other factors (such as the route of administration) also contribute towards the heterogeneity of patient responses to herbal medicines. Thus, the outcome of giving a herbal medicine to any individual is never totally predictable. Even so, some idea of the probable outcome of giving a herbal product can be based on what has been seen in other patients and what is known about the pharmacokinetics of the herbal product in question: the more extensive the data, the firmer the predictions that can be made.

Boxes 2 and *3* contain some general advice to consider when confronted with a patient who has been taking, or who wishes to take, a herbal product, or when faced with a suspected interaction between herbal products and conventional drugs.

Box 2. Advice for healthcare professionals from the Herbal Medicines Advisory Committee.

- Be aware that patients might be taking advice from unreliable sources (on the basis that "natural" means "safe") and may neglect, or not have the skills, to investigate and assess the evidence for the safety and quality of a herbal product.
- Some herbal products might contain potent or toxic ingredients that have not been disclosed in the product information.
- The number of herbal medicines registered under the Traditional Herbal medicine Registration (THR) scheme, and which therefore meet assured standards of safety and quality, is growing and enables a patient to make an informed choice. These herbal medicines can be identified by the THR logo and number on the label.
- For advice, each THR product has a summary of product characteristics and patient leaflet, which can be found on the MHRA website.

Based on information provided by the Medicines and Healthcare Products Regulatory Agency on Public Assessment Reports for herbal medicines (available at: http://bit.ly/42gDBQ [accessed 18.07.13]).

Conclusion

The use of herbal products is becoming more prevalent in the UK, as patients are increasingly interested in finding alternatives to conventional drugs to help manage chronic conditions, such as diabetes. Often this is due to a perception that herbal products have a better safety profile than conventional drugs. However, the available evidence to support such use is often conflicting or simply not available, and so there is a risk that patients might cause themselves more harm than good. While it is important to appreciate a patient's desire to avoid conventional medicines, it is also necessary for healthcare professionals to help patients understand that the decision to use a herbal product requires the same informed consideration as for conventional medicines, and could carry the same inherent risks for interactions

Box 3. General principles to remember.

- Be alert when advising patients on the use of herbal products if they are already taking conventional medicines that have a narrow therapeutic window or where it is necessary to keep concentrations of the drug or a pharmacological effect within a specific range (such as with anticoagulants and antidiabetes drugs).
- Think about the pharmacology of the herbal products and conventional drugs so that obvious problems (such as additive blood glucose-lowering effects) are not overlooked. Consider what might happen if they affect the same receptors when given together. Also be aware that many herbal medicines might affect more than one type of receptor.
- Keep in mind that older people may be at increased risk of adverse effects and drug interactions with herbal products because of reduced liver and renal function (on which drug clearance depends).

Adapted from *Stockley's Herbal Medicines Interactions* (Williamson et al, 2013).

and adverse effects. Due consideration should be given to the patient's medical condition, as well as any potential interaction with their concurrent conventional medicine regimen.

It can be difficult for healthcare professionals to gather all the necessary information in order to advise their patients appropriately on the use of herbal products, as the available clinical evidence is often sparse, and the concentrations of the constituents of a particular product might be unclear, particularly if the herb is not registered under the THR scheme. In addition, the potential for adulteration of herbal products and inconsistent quality control of herbal constituents add to the unreliability and inconsistency of using these products. Good manufacturing practice is important to ensure patients have access to good quality products, and the introduction of the THR scheme should help to assure herbal medicine quality and safety in the future. ■

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