reactions, e.g. anaphylaxis versus acute severe asthma. Serum tryptase cannot distinguish between an anaphylactic or anaphylactoid reaction, as tryptase levels are elevated regardless of the mechanism of mast cell activation. Tryptase was not measured in the patient because there was a clear causal relationship between TMP-SMX administration and the development of symptoms. The tryptase assay is available at the Allergology Unit, University of Cape Town.

Although tolerance can be induced in 33 - 100% of HIV-infected individuals, neither the mechanism of TMP-SMX hypersensitivity nor the immunological events underpinning tolerance are understood.[3] The term desensitisation implies that the underlying mechanism is IgE-mediated. As the mechanism of TMP-SMX hypersensitivity has not been fully elucidated, the terms 'graded challenge', 'test dosing' or 'tolerance induction' are preferred in the context of a TMP-SMX reaction.[2] Common features of TMP-SMX hypersensitivity such as erythematous or maculopapular eruptions, leucopenia and fever suggest a cell-, IgM- or IgG-mediated reaction. Evidence supporting the role of IgE in the pathogenesis exists, i.e. skin prick and intradermal skin test responses to sulphonamide determinants have been documented in patients who have had adverse events.[7] Non-immune mechanisms may also contribute to TMP-SMX reactivity.[8] Additional factors that may predispose HIV-infected individuals to TMP-SMX reactions include the slow acetylator phenotype, high TMP-SMX dosages, severe immunosuppression and polypharmacy.[9] It is likely that several mechanisms may precipitate these reactions.

In conclusion, a number of approaches have been used to induce tolerance. If PCPtherapy is urgently required, a 6-hour graded TMP-SMX challenge may be used.[3] Where minor reactions have occurred, cautiously 'treating through' the event will allow patients to tolerate TMP-SMX.[2,10] When TMP-SMX prophylaxis is needed a more gradual approach may be adopted as demonstrated in this case. Induction of tolerance should only be undertaken at institutions that have the facilities to manage severe adverse reactions, particularly anaphylaxis.

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Cytotoxicity of pregnancy-related traditional medicines

To the Editor: The thalidomide tragedy is witness to the fact that great care needs to be exercised in the administration of drugs to pregnant women. Approximately 80% of Zulu and Xhosa women in South Africa use traditional medications during pregnancy, so a knowledge of the toxicity of plants commonly chosen by traditional healers for pregnant women is of vital importance in assessing the potential impact they might have on the health of both the mother and the developing fetus.

The primary function of *isihlambezo* is to ensure adequate fetal growth and wellbeing and to promote general maternal health and a quick uncomplicated labour. However, there have been reports raising concern about the toxicity of some of the approximately 60 plant species used in *isihlambezo* mixtures. *Rhoicissus tridentata* extracts have been linked to a number of fatalities caused by central nervous system (CNS) depression and respiratory failure.[1,2] Animal deaths[3] have also been attributed to this species. Although the fruits of the genus *Combretum* are widely regarded as toxic, and are not consumed by wild animals or used by healers,[4] there is only one case in which the toxicity of the fruit has been clinically proven.[4] In 1996 it was reported that 5 women in Zimbabwe died after vaginal insertion of material from *Combretum erythrophyllum*, from the same genus of the Combretaceae family as *C. kraussii*.[4] The butanol extract from *C. kraussii* was found to be toxic to brine shrimp.[4] However the organic solvent butanol is not used by healers, who extract plants with boiling water. The toxicity of several other species has also been reported.[5]

We carried out a study in order to establish whether *Gunnera perpensa* (*uqobo* in Zulu), *C. kraussii Hochst* (*umdubu* in Zulu) and *R. tridentata* subsp. *cuneifolia* (*isinwazi* in Zulu), exhibited

any significant toxic effects at a cellular level. These three plants are among the six species most frequently cited[6] for use by healers in pregnancy-related traditional medicines. Such medications have been found to stimulate smooth-muscle contraction in isolated rat uterine tissue.[7-10] This supports the healers' belief that the use of *isihlambezo* leads to a faster and easier delivery. In all cases the uterotonic activity was associated with the water-soluble fractions / extracts.

The two types of cell lines used were monkey vero cells, known to be sensitive to toxins, and human fibroblasts. Cells were exposed for 24 hours to aqueous extracts of freeze-dried plant material at concentrations ranging from 500 µg / ml to 8 µg / ml. Cell viability levels were established via a colorimetric assay involving staining of non-viable cells with tryphan blue reagent (Table I and Fig. 1). At comparable concentrations *G. perpensa* extracts produced the least and *R. tridentata* extracts the most cell deaths for both types of cells. The threshold for zero cell deaths occurred for monkey vero cells at the following concentrations: *G. perpensa* 250 µg / ml, *C. kraussii* 67 µg / ml, and *R. tridentata* 8 µg / ml. At these concentrations it was found that 100% of human fibroblast cells also survived.

Table I. Cytotoxic effects of plant root extracts against the vero cell line

Plant root	Concentration (µg / ml)	Non-viable vero cells (%)
Gunnera perpensa	500	10.0
	333	2.0
	250	0
Combretum kraussii	200	10.6
	125	5.3
	100	1.9
	83	1.1
	67	0
Rhoicissus tridenata	50	28.9
	23	7.1
	10	1.2
	8	0

In order to establish whether the concentrations of ingredients in the healer's solutions were comparable to these non-toxic levels, the amounts of dissolved solids in typical medicinal solutions were calculated for each chopped or milled plant root, as well as the estimated concentration after dilution in the bloodstream, assuming a blood volume of 4 545 ml. The dose of these medications is 1 tablespoon 3 times daily, or 45 ml total per day, so there is a dilution factor of approximately 100 on entering the bloodstream. Compounds are considered to be cytotoxic when they kill 50% or more cells. It is therefore

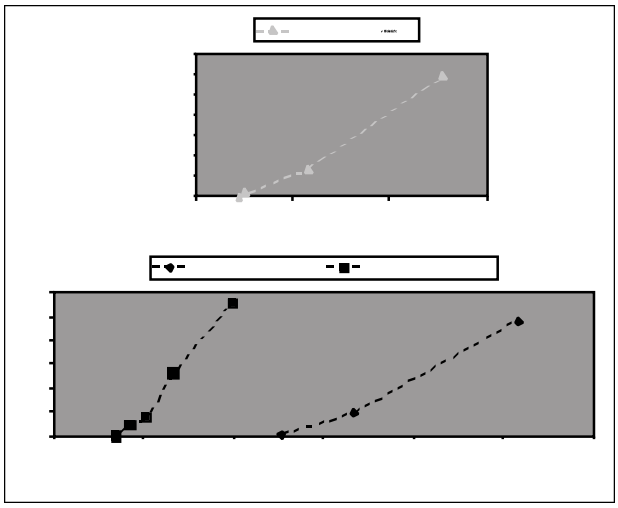

Fig. 1. Viability of monkey vero cells exposed to varying concentrations of Rhoicissus tridentata, Gunnera perpensa *and* Combretum kraussii *root extracts.*

evident, when taking into account dilution in the bloodstream, that all three plant extracts should be regarded as completely non-toxic. Their estimated concentrations in the bloodstream were 4.6 µg / ml for *G. perpensa*, 8.9 µg / ml for *C. kraussii* and 6.1 µg / ml for *R. tridentata*. These all fall below those concentrations, resulting in zero cell deaths (TableI). Furthermore, another roughly 10-fold dilution would occur throughout the various organs and tissues, leading to the conclusion that these plant extracts should be considered non-toxic at a cellular level. However, we advise that *R. tridentata* be used medicinally with caution. In addition to these cell viability results, it has also been found that *R. tridentata*, together with *Clivia miniata* (*umanyimi*) and *Agapanthus africanus* (*ubani*), significantly augment the initial response of the uterus to oxytocin, and therefore must be considered to have the potential to cause uterine hyperstimulation and its associated toxicity.[6] Since concentrations of uteroactive ingredients in *R. tridentata* increase in the summer and autumn seasons and there are also significant regional differences in its uterotonic activity,[11,12] traditional healers need to be aware of these variations in the light of possible uterine hyperstimulation, and alter dosages accordingly.

The vast amount of research by pharmaceutical companies regarding the safety of drugs for pregnant women is in stark contrast to the paucity of knowledge about herbal remedies, even though the latter are used by the majority of women in South Africa. An international workshop on the use and safety of medical herbs recommended that these therapeutic herbs should be tested, like other pharmaceuticals, to characterise their acute and chronic toxicities.[13] Herbal medicines are used

by millions of people throughout the world and some countries such as China and the USAtest and monitor the use of such medicines, informing health care providers of the benefits and risks involved. There are at least eight research institutes devoted to traditional medicines in China, and in America a branch of the National Institutes of Health oversees this type of research. The Kenyan government plans to table a bill in Parliament which will, if it becomes law, allow herbal medicines to be available in government hospitals for the first time.[14] This proposal is backed by the World Health Organisation (WHO) which recognises traditional medicine as a solid amalgamation of dynamic medical know-how and ancestral experience.

This structured approach needs to be developed more fully in South Africa to ensure both efficacy and safety in the use of natural medicines. An exciting move in this direction was the recent opening of Mwelele Kweliphesheya (crossing over of two medical cultures) at Cato Ridge, KwaZulu-Natal, for cultivation of medicinal plants. A traditional medicines hospital as well as a college for training of healers is also planned, and the project has provincial government support. Medbase, a database of the 260 most important medicinal plant species in South Africa, has also been published by the National Botanical Institute and the Department of Environmental Affairs and Tourism. Ultimately this rich heritage of traditional knowledge, the source of so many modern drugs, should achieve formal recognition by central government.

Our gratitude is expressed to the National Research Foundation for financial support for this study and to Mr T Venketsamy who conducted cell viability tests at the Virology Department, University of Natal. Protas Cele of the Traditional Healers' Association is gratefully acknowledged for his advice on medicinal preparations, as well as for the supply of plant material.

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