

Combinations of Natural Products: Opportunities and Dangers**Paul F. Davis**

Bioactivity Investigation Group (BIG), Wellington School of Medicine and Health Sciences,
Wellington, New Zealand. E-mail: pdavis@wnmeds.ac.nz

ABSTRACT

The use of medicinal food, food supplements and nutraceuticals is steadily increasing worldwide. These products are derived from a variety of sources of ethnic traditions and new research findings. They are being utilised in a diverse range of preventive and therapeutic situations. Because of this increased interest there is greater use of multiple natural products simultaneously. The use of combinations needs to be treated with circumspection. Mixing may have no unexpected consequences or it may have rather unanticipated beneficial outcomes. Just as likely are deleterious effects from combining the intake of natural products. Recent research has been quite useful in the characterisation of the consequences of some of these combinations and examples will be presented.

INTRODUCTION

The use of natural products has a very long history. Traditions and records have clearly shown that humans have tried to maintain a healthy status through the eons. This has included both preventing the onset of diseases and chronic conditions and the treatment of maladies, illnesses and infections.

In these earlier times this was primarily achieved by finding food products and edible materials that provided these attributes. There were no pharmaceutical industries or chemical synthetic production plants. Rather people developed products, remedies and treatments using animal, plant, fish and birds as the source. Once a satisfactory treatment was developed, it became a tradition of that ethnicity and culture. It was passed on for many generations.

Historical Examples

For example it is well-known that what we know as traditional Chinese medicine had its origins probably 3,500 years ago. Although it was probably not medicine as understood in the 21st century but by the time of the Zhou dynasty (2,700 years ago) there were treatments being repeatedly prescribed (1).

In the Arab world there is also a long tradition. Pharmacy was established as a distinct profession as far back as 1,800 years ago. They had individual drugs as well as combinations of products that they had derived for the treatment of many conditions (2). By the time of the Samanids (approximately 1,100 years ago) a range of therapies were very well established. Two names from that period that are frequently quoted are Muhammad Zakariyya Razi and Abu Ali ibn Sina (3). They are important as much of their knowledge and teaching has been recorded in books and was the basis of the current Middle Eastern therapies.

As this is an international conference, a third example of traditional usage from another part of the world is appropriate. There is a well-established repertoire of medicines by the Incas of South America. In Bolivia the history among certain tribal groups such as the Kallawayas even precedes them by another 1,000 years (4).

The fact that these approaches have such a long history in traditional knowledge suggest that they do have efficacy. This has been recognised by many 'consumers' and so is a factor in the current level of interest in this

approach to health and medical treatments.

Current Usage

In the 21st century there is a steadily increasing usage of natural products either as preventatives or therapeutics. These take a variety of forms including nutraceuticals, functional foods, food supplements and medicinal foods. In the United States of America, for example, the market in 2001 was estimated to be worth \$18 billion and growing by at least 20% per year (5).

With this increasing use and popularity, there is a tendency for individuals to take a variety of these natural products. Seldom is a patient taking just one supplement or product. In fact people are often taking a large number of remedies simultaneously aimed for treating a variety of different conditions and situations. Additionally there are recommendations by professionals that a combination of products is likely to be beneficial. But more frequently the selection of choice of combinations is not based on sound rigorous research. Rather they are often based on anecdotal information. This data is gathered from multiple and diverse sources. One hears or learns that a particular treatment is likely to be beneficial for a particular situation. Later the same individual learns of another treatment that has been used successfully by someone else for the same or a closely related condition and so decides to take that as well. And so it grows and before long, this same individual is taking a multiple number of items. As you will readily appreciate the situation is compounded if the person has more than one medical or health condition that needs attention and treatment and even more so if the individual is also taking prescription pharmaceutical items.

Combinations

This raises the question as to the nature of the interactions between these various supplements and medicines might be. For example if it is known that one product is beneficial for a particular situation and a second product is useful for a second condition, does taking them benefit the 2 conditions or is the activity of one of them compromised or even worse do they result in some unexpected adverse effect?

For example **garlic** has been traditionally used for a number of conditions including hypertension, cardiovascular conditions, a number of neoplasms and variety of infections. **Cod liver oil** is reputed to be useful in a variety of diverse applications including cancers such as B-cell lymphoma, prostate and breast cancer, hypertension, hypertriglyceridemia, arthritis and cardiovascular diseases. However it has been reported that use of the two of them together can have anti-coagulant effects. However this is anecdotal rather than being from a designed clinical study (6).

It is likely that people, particularly older ones, may have multiple conditions requiring attention and treatment. So the likelihood of them taking more than one natural remedy is high.

A second example. Ginger (*Zingiber officinale*) has widespread applications. One database has listed more than 30 reported or suggested uses (7). Therefore it has common usage. By and large it has been regarded as safe. There is published evidence to support this assumption. However there is also published data that it can inhibit thromboxane synthetase and therefore that it can decrease platelet aggregation (9). As well as there being a risk for patients who are taking anti-platelet or anti-coagulant prescriptions, there may well be a greater risk if they are taken concomitantly with other natural and herbal supplements with such anti-coagulant or anti-platelet potential. Therefore, there is a risk for some individuals if they are consuming ginger and also other natural products such as angelica, garlic, ginseng panax, red clover or tumeric.

While this view is somewhat negative, the risks for individuals and the liabilities of producers and marketers has risen significantly. This is especially so with the large increase in international indirect sales via the telephone, the internet etc.

However there is another aspect of combinations that needs to be commented on. In addition to the situation where the individual consumer or patient chooses his or her own mixture of treatments as just illustrated, there is also the situation where the marketer does the combining.

While many of these combinations are beneficial, there are also instances where they are detrimental. For example, a product available here in Korea and also in Japan and China is being used by cancer patients, particularly terminal ones. It has an oil derived from shark as one constituent. This has been shown to have significant anti-angiogenic properties as well as anti-inflammatory activity. Another β -glucan rich mushroom derivative has known immune-enhancing activity. However the 2 together are having a significant effect on tumours resulting in a reduction in the proliferation rate of primary tumours and also the regression of metastases. The effect of the combination is greater than predicted from the known activities of the 2 components alone. As well, neither of them alone or together appear to have anti-tumour or cytotoxic activity. I should add that this combination is being marketed as a therapeutic treatment.

In contrast, research we undertook that was centred around echinacea and products which combined this plant with a range of other known herbal and dietary supplements revealed some unexpected findings. Echinacea is widely promoted as an immune enhancing product. The active constituent is widely believed to be cichoric acid. Echinacea extract is able to stimulate T-cell proliferation. There are no widely reported adverse reactions when coupled with other herbal supplements. Coupling it with other reputed immune stimulants resulted in an additive effect. However there are other combinations of echinacea with other immune promoting products that resulted in a suppression of the stimulatory effect. That is, the combinations may be regarded as slightly suppressive. What is somewhat concerning about this data is that all these combinations of echinacea and other additives were readily available through retail outlets.

A third example that I would give is based on research performed by our group. We were researching a particular lipid-rich extract from sharks which was found to be strongly anti-angiogenic. It was decided to investigate further the potential applications of this extract. Its potency meant that it needed to be diluted so that a practical concentration could be prepared. It was decided to use a commonly available cooking (vegetable) oil such as olive oil as diluent as they were known to have no pro- or anti-angiogenic activity. However when the fish oil was diluted 10-fold with olive oil, its activity approximately doubled in a tissue culture model but it stimulated the effect of the shark lipids by about 6 times when evaluated in animals. Thus the dilution of the biologically active shark lipids with an inactive carrier resulted in a massive synergistic anti-angiogenic activity. So here is a beneficial outcome from the coupling of 2 natural products. This has led to a product that is now being used in a number of countries for treating cancer patients.

The risks and dangers associated with the use, particularly long-term, of prescription pharmaceuticals are quite widely publicised. A very recent example has been the use of COX-2 inhibitors when one of the largest selling ones was withdrawn because of the risk of cardiovascular complications, particularly cerebral. In a similar vein the potential problems that may arise when 2 or more prescription medicines are consumed contemporaneously are often well annotated. This is because regulatory authorities frequently require such data. Additionally a number of these therapies are for the treatment of chronic conditions which frequently are an affliction more prevalent in the elderly who may be suffering from several unrelated such conditions. Consequently these patients

are expecting to be able to have treatments providing for their several medical conditions.

However with the increased usage of 'over the counter' products, the possibility that patients may be taking both these and also prescribed drug therapies is real. Often when a drug is being prescribed, the patient does not reveal to the clinician or is not asked about anything else that he or she might be taking. Alternatively the patient may decide to include a non-prescription item in their treatment subsequent to commencing the drug protocol.

Obviously there are risks associated with this. Unfortunately there has been considerably less research undertaken in this area of drug and natural product interactions than in the area of drug drug combinations. But there is an increasing number of research laboratories undertaking research specifically on such interactions.

By way of examples it is known that the activity and effects of the anti-thrombotic, anti-coagulant compound warfarin are decreased by American ginseng, St John's wort and Coenzyme Q10 (7). But just to show how unclear and muddled this topic may be, Siberian ginseng is a different herb and I have been unable to find any data about it in relation to interaction with warfarin. Yet there is widespread use of the Siberian ginseng and so no considered advice about it can be provided.

But just to show that not all combinations of drugs and natural products are detrimental. It is known that warfarin's effects are increased by a number of other herbs including garlic, ginger, ginkgo, fish oils and up to 60 other products.

CONCLUSION

So, in summary the first point is that all natural products are biologically active. They can therefore interact with a range of cells and pathways just as any other products, including a pharmaceutical, can. They can also modulate the activity of other materials or can have their activities altered. Sometimes these changes can be unpredictable.

Much care and caution is needed when they are being used. A similar approach to that used for determining the application of applications of pharmaceuticals is required here also.

Finally it is very apparent that there is a very considerable lack of reliable data and information in this area. So it is urgent and imperative that sound reliable research be initiated.

REFERENCES

1. Felt RL. 2001. *The Ancient History of Chinese Medicine*. Paradigm Publications, Brookline, USA.
2. Nuraliev Y. 2002. Persian Medicine and Medical Care Under the Samanids (874-999AD). <http://medanth.members.easyspace.com/persianMedicine.htm>.
3. A History of Muslim Pharmacy. 2004. <http://medanth.members.easyspace.com/persianMedicine.htm>.
4. Lunny VN. 2002. Traditional Herbal Medicine in Bolivia, South America. *Positive Health*.
5. NBJ's Annual Industry Overview. VII. *Nutrition Business Journal*, (May-June, 2002). 1-48.
6. Natural Medicines Database Update August 10, 2004. naturaldatabase.com.
7. Natural Medicines Database. naturaldatabase.com.