Synergy: Interactions within Herbal Medicines

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Introduction

Synergistic interactions between the components of individual or mixtures of herbs are considered to be a vital part of their therapeutic efficacy; however until recently there has been very little evidence to demonstrate what herbal practitioners have always believed. Sometimes it seems as if doses of supposed active constituents are too low to have an effect, and in the absence of clinical proof this has led sceptics to dismiss these medicines as mere placebos. There is another complication to this aspect, in that phytomedicines often take a while to produce a measureable improvement, appearing to have a cumulative effect and for this reason long-term therapy is routine, and of course there is no reason why these properties should not co-exist in the same preparation! In fact the mechanism of action of most phytomedicines is still unknown and there are several instances of a total herb extract working better than an equivalent dose of an isolated compound, for which we have no real rationale. Some of these will be outlined in this paper. Speculation as to the reason for this, whether it involves synergy, enhanced bioavailability, cumulative effects or simply the additive properties of the constituents requires further research, probably involving a thoroughly new approach, as has been described by Wagner (1999). Until the answers to some of these questions are found, it would be logical to suggest that for long-standing or more difficult disorders, patients should ideally see a practitioner for a diagnosis and holistic approach to their condition, leading to a tailor-made prescription taking into account the various manifestations of their symptoms and perceived causes. Those who have a condition suitable for self-medication, such as low mood (mild depression), menopausal symptoms, minor aches and pains and so on, should have access to good quality products either of a traditionally well-known, licensed formulation, or a new standardised phytomedicine which has been clinically assessed. In all cases synergy will be playing a part in both the prescription and the purchased product.

As well as European traditional medical herbalism, Oriental systems such as traditional Chinese medicine and Ayurveda generally assume synergy to be taking place, and it is an intrinsic part of their philosophy. Combinations of herbs are normal and may be either historical formulations, which have been developed by empirical observation or are put together for an individual patient.

Despite the complicated nature of the interactions in phytomedicines, it would surely be useful to examine the concept of synergy in an attempt to reduce side effects and improve therapeutic success. The approach taken by herbalists to skin disorders such as eczema differs radically from conventional treatment, which usually involves topical application of corticosteroids with their inherent disadvantages, and may lead eventually to the use of cytotoxics in refractory cases. In contrast, the multi-targeted approach of the herbalist must surely be preferable, and the Chinese herbal remedy containing multiple ingredients used to treat eczema, is a good example of this.

Herbal products with reputed synergistic activity should obviously not be used if they are toxic herbs used in conditions where the dose is crucial - for example foxglove is not a suitable herbal remedy for congestive heart failure, as the therapeutic index is so low, but hawthorn certainly is because of its more gentle, cumulative (and probably synergistic) effect. Until the nature of the interaction is known and

extracts standardised to incorporate what is known, care must be taken with potent herbs, although there is no point in ignoring the wisdom of experience! It does emphasise the unique qualities of herbal medicines and can give lessons in managing disease effectively and with minimal adverse effects.

Defining and proving synergy

This is much more difficult than would be first thought, since synergy has a precise mathematical definition according to the method used to prove it. There are only a few well documented instances available from the literature, and there are several reasons for this, the main one being the difficulty of proving such effects, since to do so would necessitate the testing of each individual constituent and comparing the activity with an equivalent dose in the mixture. This is an immense undertaking and prohibitively expensive in terms of time and money and has therefore rarely been done, although some recent experiments confirm its existence and will be described later. We therefore tend to use the term 'polyvalent action' to denote an improved and cooperative sort of effect without necessarily qualifying it, to try to preempt some of the criticisms we face, as it often seems as if anecdotal evidence is only ever accepted when it is negative, rather than positive. The general understanding of synergy is that it is an effect seen by a combination of substances being greater than would have been expected from a consideration of individual contributions.This can apply to either an increased therapeutic effect, a reduced profile of side-effects or, preferably (and logically), both. Within a herbal mixture, this may be very difficult to describe accurately as there are present constituents of which we know very little, either chemically, pharmacologically or even quantitatively. Antagonism is much easier, being the opposite, ie a reduced effect from that expected, with few questions asked as to the mathematical derivation!
To briefly summarise the measurement of synergy, the definitions of Berenbaum are the most useful:
1. *Summation of effects:* this is when the total effect of a combination is greater than expected from the sum of its effects. In effect:
E (da,db) = E (da) + E(db)
where E = the observed effect, and da and db are the doses of agents a and b
As it depends on the mechanism of action of each component, and assumes a linearity of response for each, it is largely irrelevant when dealing with complex mixtures, it will not be discussed further.
2. *Measurement of a fixed dose of one on the dose-response of another component:* This has similar disadvantages to the 'summation of effects' model.
3. *Comparison of the effect of a combination with that of each of its components:* This seems very logical until examined further. It was originally suggested by Gaddum, and says that synergy is deemed present if the effect of a combination is greater than that of each of the individual agents - ie
E(da,db) > E(da), and E(da,db) >E (db)
This method is independent of any knowledge of the mechanism of action, and seems logical at first glance, but is easily destroyed by looking at Berenbaum's example: if two men, working separately, can each cut down 10 trees in a day, but together can cut down only 15, then this would actually fulfil Gaddum's mathematical requirements, but is obviously a nonsense.
4. *Isobole method*: this is now the method of choice, and although more complicated, is independent of the mechanism of action and applies under most conditions. It also makes no assumptions as to the behaviour of each agent and is therefore applicable to multiple component mixtures. The example of the ginkgolides given later was done by this method and will serve to illustrate it. An isobole is an 'iso-effect' curve, in which a combination of ingredients (da,db) is represented by a point on a graph, the axes of which are the dose-axes of the individual agents (Da and Db). If the agents do not interact, the isobole (the line joining the points representing the combination to those on the dose axes representing the individual doses with the same effect as the combination) will be a straight line. If synergy is present, the amount needed by the combination to produce the same effect will be less than that for the individual components and the curve will be 'concave up'. The opposite

applies for antagonism, which produces a 'concave down' isobole. It is quite possible to have synergy at one dose combination and antagonism at another, with the same substances and this would give a complicated isobole with a wave-like or even elliptical appearance.

To complicate matters further, herbalists use preparations and mixtures which are are not necessarily intended to target a particular enzyme or biochemical system (Mills and Bone 2000); making synergy even more difficult to identify. The use of phytomedicines has been described as the 'herbal shotgun' approach, as opposed to the 'silver bullet' method of conventional medicine (Duke and Bogenschutz-Godwin 1999) to distinguish the multitargeted approach of herbals from a specific enzyme or receptor target of a synthetic drug. Phytotherapy is a holistic approach whereby treatment is approached from several angles - and is not much different to some forms of so-called 'conventional medicine' where several drugs are used to treat a particular disorder: cancer would be a prime example, and many types of mental illness are also treated in this way. Something as simple as including a laxative in a preparation for haemorrhoids would fulfil this definition and synergy does not need to apply in any way at all.

It is still routine for scientists to investigate and extract medicinal plants with a view to finding the single chemical entity responsible for the effect, and this may lead to inconclusive findings. If a combination of substances is needed for the effect, then the bioassay-led method of investigation, narrowing activity down firstly to a fraction and eventually a compound, is doomed to failure, and this has led to the suggestion that the plants are in fact devoid of activity. An example of this would be with *Kigelia pinnata*, where fractionation destroyed the cytotoxic effect (Houghton, 2000). Only clinical trials can dispel these misconceptions, but they are expensive. Instead it should be anticipated that mixtures may play a part, and when activity is thought to be lost during purification, synergy should be suspected. This could be the point at which a search for synergy in particular could be instigated.There are other sound reasons for not always isolating or fractionating a plant extract, and together these may be summarised as follows:

1. **Synergism**: if synergism is known or suspected to be present, the mixture is necessary for the therapeutic effect. Known examples include *Ginkgo biloba, Artemisia annua, Cannabis sativa* and kava, *Piper methysticum*, but there are probably many more.

2. **Unstable constituents**: sometimes the presence of the whole plant material, which may contain for example antioxidants, may 'protect' the actives from decomposition. Examples here would be: valerian, *Valeriana* spp.; garlic, *Allium sativum*; ginger, *Zingiber officinalis*; hops, *Humulus lupulus*. In the case of garlic, perhaps the the precursor alliin could be described as a pro-drug, or even a drug delivery system

3. **Unknown active constituents:** even if some of the chemistry is know, the actives may not have been completely identified. Examples include raspberry leaf, *Rubus idaeus;* chasteberry, *Vitex agnus castus; Passiflora; Crataegus* and many others

4. **A range of actives** (which may or may not indicate synergy): *Echinacea, Harpagophytum procumbens, Cynara scolymus, Hypericum perforatum, Glycyrrhiza glabra* essential oils and many others. These may well (and do) have documented clinical activity and there is little incentive to fractionate, isolate and characterise, and they may be acting synergistically or additively.

Any or all of the above may be operating at the same time. Other interactions found with plant drugs may occur because of enzyme induction or inhibition and increase or reduction of bioavailability. Ayurveda, one of the oldest systems of medicine in the world, uses many fixed combination formulae and one of the ingredients 'Trikatu' features in many of them. This mixture contains black pepper, *Piper longum*, and ginger, *Zingiber officinalis.* It is only recently that this combination has been investigated scientifically

and reasons put forward for its inclusion. Pepper contains the alklaloid piperine, which is known to increase the bioavailability of a number of drugs such as vasicine (also known as peganine), an antiasthmatic alkaloid from *Adhatoda vesica* (Johri *et al* 1992).

A number of theoretical possibilities have been put forward but it remains to be seen whether they occur in clinical practice or not, and it is often not possible to predict these. Some will appear only after prolonged administration of the combination, and some with only high doses. It is surprising that more are not observed, which may of course be related to the fact that synergistic effects will require low doses.

In vitro and other experimental evidence

Ginkgo biloba

In one of the few published examples, *Ginkgo biloba* has been assessed using an *in vitro* platelet aggregation test. The ginkgolides are known to be PAF antagonists, which is one of their mechanisms of antiinflammatory activity, and now a synergistic interaction between ginkgolides A and B has been shown by Wagner's group in Munich. In this case, a positive interaction was shown by an isobole curve using a 50% mixture of the two (Fig1). The presence of the other ginkgolides and the ginkgoflavones is also likely to have an affect on the overall activity, and this is confirmed by the example Wagner quotes: a mixture of ginkgolides A, B and C at a dose of 100-240mg can generate a PAF-antagonizing effect in humans (Chung et al 1988); however a dose of 120mg of a standardized Ginkgo extract containing only 6-7mg of ginkgolides, together with bilobalide and flavonol glycosides, has a similar effect (Wagner 1999). The implications of these results are of course that an isolated ginkgolide would be less therapeutically effective than a mixture, despite the fact that ginkgolide B is known to be a specific PAF antagonist and has been the subject of many pharmacological experiments. So although a 'magic bullet' has been discovered in the herb, it is still much more effective when used in the extract, ie the 'herbal shotgun' approach is vindicated here.

Kava, *Piper methysticum*.

Kava is a well-known psychoactive herb used in the South Pacific as a ceremonial drink, sedative and mild euphoriant. It also has a well-established place in herbalism for the treatment of mild anxiety states as an alternative to the benzodiazepines (Schultz *et al* 1998). The chemical composition is well known but the contribution of each to the overall activity is not, although synergy is implicated in several ways: the anticonvulsant activity of the kavalactones yangonin and desmethoxyyangonin was found to be superior when given with other kava constituents; and in a separate experiment when a reconstituted mixture of individual constituents was tested and related to the activity of the most potent compound (dihydromethysticin) synergy was again indicated. Details of these experiments are given in the review by Singh and Blumenthal (1997).

Liquorice, *Glycyrrhiza glabra*.

Liquorice provides a number of examples of both synergy between its own constituents as well as with other herbs. Blood levels of glycyrrhizin are lower, due to reduced absorption, if it is taken as part of an extract rather than as an isolated compound (Cantelli-Fort *et al* 1994). It has also been shown that the crude extract of liquorice inhibits angiogenesis, granuloma formation and fluid exhudation in a mouse model of inflammation, as does isoliquiritin and related compounds, whereas glycyrrhizin and glycyrrhetinic acid tend to promote angiogenesis (Kimura *et al* 1992). These are obviously opposing actions within the herb itself, and there is then the situation where liquorice is added to so many mixtures in Chinese medicine as a synergistic agent, both as a potentiator and detoxifier.These effects are now becoming better understood, and it is known that liquorice potentiates compounds such as paeoniflorin as a neuromuscular blocking agent, whilst affecting intestinal absorption of toxic substances such as the aconite alkaloids (Miaorong and Jing, 1996). This gives liquorice a useful role in detoxification and suggests further investigation would be rewarding.

Marihuana, *Cannabis sativa*

Although cannabis has a rather tainted record as a medicine, recent research is confirming its role as a useful therapeutic agent in chronic conditions such as rheumatoid arthritis, AIDS and multiple sclerosis (MS). Documented reports of interactions within the single herb include that of marijuana, *Cannabis sativa*, where levels of tetrahydrocannabinol (THC) in the brain can be elevated by cannabidiol (Zuardi *et al* 1982). It has long been known that THC alone can induce anxiety which can be attenuated by the presence of cannabidiol (CBD) in the herb, and sufferers of multiple sclerosis (MS) seem to prefer the herb to the isolated constituents for relaxant activity (Williamson and Evans 2000). We now have additional evidence to show that the effect of the herb is both qualitatively and quantitatively different to isolated THC, in that the herb extract is a better antispastic agent than THC as well as having an effect on anadamide transport which is not shown at all by THC (unpublished observations). This synergistic effect will become very important if and when cannabis becomes a medicine, as it will reduce the psychotropic side effects which are an impediment to clinical use.

Valerian

An extract containing valtrate, isovaltrate, valerenone and valerenic acid has been shown to reduce glucose consumption in the brain, although none of these substances does so individually (Holzl 1997). Of course there may be a minor, highly potent compound responsible for this activity, but given the amount of chemical research which has been carried out on valerian this seems unlikely!

Flavonoids

Flavonoids are present in many phytomedicines and foods, and are known to have various activities such as enzyme inhibition. It is now thought that they may have a role to play in increasing the biological activity of other compounds by synergistic or other mechanisms. Two pieces of research support this theory: an *in vitro* antimalarial test showed that the activity of artemisinin was enhanced by the presence of the flavonoids artemetin and casticin (Phillipson 1999) and pairs of flavonoids, taken from genistein, baicalein, hesperetin, naringenin and quercetin, were shown to be synergistic for inhibition of growth of a human breast cancer cell line. The only pair which did not have this combination effect was naringenin and hesperetin which are chemically very similar (So *et al* 1996).

Essential oils

Ginger, *Zingiber officinalis*, has been used as an antiulcer treatment and synergy is implicated in its effect. An extract was fractionated and assayed, and 97.7% of the activity found to reside in the fraction containing a-zingiberene, b-sesquiphellandrene, bisabolene and curcumene, despite the fact that it accounted for only a small proportion of the total; the effect however was 66 times that calculated from a summation of the individual ingredients and again synergy is implicated (Beckstrom-Sternberg and Duke 1994). Many members of the Labiatae contain antioxidants and essential oil components and many of these are anti-cholinesterases. A combination of these, which would also apply to sage, may account for the claim that rosemary is the 'Herb of Remembrance' (Duke and Bogenshutz-Godwin 1999, Perry *et al* 2001). Other instances of synergy with phytochemical antioxidants such as apocynin have also been described (Beukelmann *et al* 1995).

In our own work with essential oils, where lethality on human lice was measured, we have found a type of activity which could possibly contribute to a mechanism of synergy. Individual terpenoids were first screened for activity against lice and their eggs, and the most potent then subjected to studies on their mechanism of action. This was done by looking at GABA-ergic activity, a mechanism by which many insecticides exert their effect. Although no agonist activity was found, a potentiation of the effect of GABA was observed which was both large and dose-dependant (Priestley *et al* 1999). This is thought to be due to an allosteric modulation of the GABA receptor and has been confirmed in human GABA receptors also (unpublished observations). Studies continue to see how this could affect concurrent

administration of other drugs.

Synergy implicated in mixed-herb formulations. Apart from the inclusion of liquorice and pepper in Oriental formulations as already described, synergy between different herbs in a formulation is also shown pharmacologically by a combination of nettle, *Urtica dioica*, and pygeum bark, *Pygeum africanum*, which is taken for benign prostate hyperplasia. Here a combination of both inhibits 5-a-reductase and aromatase more significantly than the sum of either alone (Hartmann *et al* 1996). Other experimental evidence of interaction between herbs has been provided by Phillipson (1999) where a clinically successful formulation of Chinese herbs to treat eczema (Sheehan and Atherton 1992) was investigated phytochemically and pharmacologically, and activity appeared to have been lost during fractionation.

Clinical evidence

Valerian and Kava

Clinical results are of course the most important indicator of efficacy of combinations, and despite its inherent difficulties and costs, this type of testing has recently become the focus of more interest. Until recently the evidence has been mainly anecdotal or by inference, but there are a few clinical trials which demonstrate the phenomenon fairly well. A combination of kava and valerian, *Valeriana officinalis*, appears to be superior for the treatment of stress-induced insomnia than either herb alone (Wheatley 2001). This study was an open, cross over, trial involving 24 patients, and various methods for the measurement of stress, such as personal, social and other life events were measured. Insomnia was also evaluated using the latency period of getting to sleep, the hours slept and mood on waking. Although preliminary in nature, the results certainly suggested that synergism between the two preparations was taking place.

Ginseng and Ginkgo

In a double-blind, crossover trial using 20 young, healthy volunteers, a product containing ginseng, *Panax ginseng*, with ginkgo, was recently demonstrated to be more effective in improving cognitive function than either alone, as measured by the performance in various arithmetic tasks. (Scholey and Kennedy 2001)

Conclusions

As herbal medicine continues to increase in popularity it has become vital to educate the medical and scientific establishment and show that there are some features which are unique to phytotherapy and which contribute both to efficacy and safety. One of these is the concept of synergy, in that a plant extract is more than the sum of its parts, which will substantiate the perception that natural medicines have something special to offer. This is already accepted by patients and practitioners, but we now have an opportunity through further testing to prove that it is a true phenomenon which should be appreciated and utilised for therapeutic benefits.

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