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REVIEW

# Synergy and other interactions in phytomedicines

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## Summary

**Synergistic interactions are of vital importance in phytomedicines, to explain difficulties in always isolating a single active ingredient, and explain the efficacy of apparently low doses of active constituents in a herbal product. This concept, that a whole or partially purified extract of a plant offers advantages over a single isolated ingredient, also underpins the philosophy of herbal medicine. Evidence to support the occurrence of synergy in within phytomedicines is now accumulating and is reviewed here. Synergistic interactions are documented for constituents within a total extract of a single herb, as well as between different herbs in a formulation. Positive and negative aspects of interactions are discussed together with the methods used to identify and measure synergy. The evidence is divided into experimental, *in vitro* instances, as well as clinical examples where available. Herbs discussed include *Ginkgo biloba, Piper methysticum (Kava-Kava), Glycyrrhiza glabra, Hypericum perforatum, Valeriana officinalis, Cannabis sativa, Salix alba* and others.**

**Key words:** synergy, phytomedicine, herbal interactions

## Introduction

Many of the most effective phytomedicines are on the drug market as whole extracts of plants, and practitioners have always believed that synergistic interactions between the components of individual or mixtures of herbs are a vital part of their therapeutic efficacy. Until fairly recently there has been little clinical evidence to demonstrate conclusively that this is the case, and it very often it is argued that the dose of supposed active constituents is too low to exert any therapeutically relevant effect at all. In the absence of clinical proof this has led sceptics to dismiss these medicines as placebos, and it is compounded by the fact that there may be result in a measurable efficacy only after continuous administration, which might be due to a cumulative effect. For this reason long-term therapy is routine, but this is not a unique property of natural products and is found in conventional medicines such as the synthetic antidepressants where several weeks of treatment may be necessary before a clinical improvement is seen. The use of drug combinations is also not confined to herbal products, and for example cancer chemotherapy, the treatment of HIV and hypertension, routinely employ drug combinations consisting of two or more individual substances. In fact the mechanism of action of many phytomedicines is still unknown and there are several instances of a total herb extract showing a better effect than an equivalent dose of an isolated compound, for which we have no real rationale. Some of these will be outlined in this review. Speculation as to the reason for this, whether it involves synergy,

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enhanced bioavailability, cumulative effects or simply the additive properties of the constituents requires further research. It will probably involve a thoroughly new approach, for instance by investigating mechanisms using new molecular biology techniques for the isolated ingredients individually and in combination, as has been described by Wagner (1999). In this respect, we are only at the beginning of an interesting new research field, which should shed light on how these remedies work, and ultimately result in reduced side effects and a better therapeutic success.

## Positive and negative aspects of herbal interactions

In general, synergistic effects are considered to be positive, with the low doses used perceived as a benefit, although it is obvious that there may also be negative aspects. Adverse reactions (ADR's) tend to be more apparent with combinations of herbs or interactions with prescribed synthetic medicines, but clinical manifestations of do not seems to be common, which may be due partly to a lack of reporting of ADR's for herbals. Important positive interactions would include those of Ayurveda, which uses many fixed combination formulae with "Trikatu" featuring in many of them. This mixture contains black pepper, *Piper longum*, and ginger, *Zingiber officinalis* and although an ancient recipe, it is only recently that this combination has been investigated scientifically and reasons put forward for its inclusion. Pepper contains the alkaloid 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). It may be that this applies much more commonly than has been previously thought and has implications for nutrition. Unwanted interactions for example would be the presence of tannins in a herbal drug, which may hinder the absorption of proteins and alkaloids, or the induction of enzymes such as cytochrome P450 which may accelerate drug metabolism resulting in blood levels of actives too low for a therapeutic effect. This could have more serious consequences, for example in the case of St John's Wort (SJW), *Hypericum perforatum*-extract, where interactions with oral contraceptives have been reported, albeit infrequently. For further references negative interactions of herb drugs with synthetic drugs see Ernst et al.1999. However the synthetic drugs involved are usually well known for their potential to interact and patients taking them are warned not to combine their medication with any other unless under medical supervision. The most important drugs from this point of view are cyclosporin used as an immunosuppressants after transplantation, warfarin as an anticoagulant and the protease inhibitors used to treat HIV infection. In addition, herbal products with reputed synergistic activity should not be used if they are potent herbs used in conditions where the dose is crucial. Foxglove, *Digitalis*, is not a suitable herbal remedy for congestive heart failure and heart insufficiency grade I and II according to the NYHY, as the therapeutic index is so low, but hawthorn certainly is because of its more gentle, cumulative, and probably synergistic, effect.

## Differences in the approach to treatment

As well as with European phytomedicine, Oriental systems such as traditional Chinese medicine and Ayurveda generally assume synergy to be taking place, and it is an intrinsic part of their concept or philosophy of therapy. 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. To complicate matters further, herbalists use preparations and mixtures which are not necessarily intended to target a particular organ, cell tissue or biochemical system , 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 multi-targeted approach of herbals from the specific enzyme or receptor target of a synthetic drug. Something as simple as including a laxative in a preparation for hemorrhoids would fulfil this definition and synergy does not need to apply in any way at all. There is also the approach taken by herbalists to skin disorders such as eczema where the approach differs radically from conventional medicine. In Western medicine, the treatment often involves topical application of corticosteroids, which are symptomatically effective but have inherent disadvantages. In contrast, the Chinese herbal remedy containing multiple ingredients used to treat eczema (Sheehan and Atherton 1992) is a good example of the herbal approach. However, until the nature of the interaction is explained and extracts standardised to incorporate what is known, care must be taken. Further research is therefore paramount to emphasise the unique qualities of herbal medicines and to rationalize the therapeutic effect of the complex mixtures of single drugs or constituents; in addition results can be extrapolated to other medicines, and can give lessons in managing disease effectively and with minimal adverse effects.

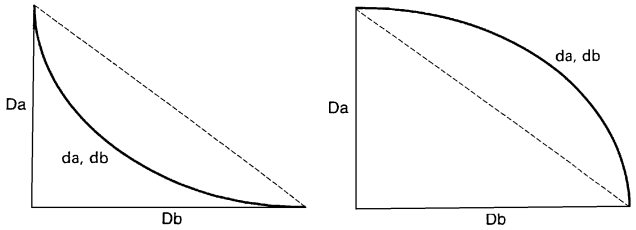


**Fig. 1.** The Isobole method of identifying synergy. Da and Db are the individual doses of a and b; da and db are the doses of a and b in the mixture. The dashed line shows zero interaction, i.e. all combination doses to produce this effect if no interaction occurs. **a.** Effect of Synergy: the 'Concave' Isobole. Synergy is shown by the solid curve. **b.** Effect of Antagonism, the 'Convex' Isobole. Antagonism is shown by the solid curve.

## Defining and proving synergy

This is difficult, 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 in methodology of proving such effects. To do so would necessitate the testing of individual constituents 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 (synonyms are: mulitvalent or pleiotropic) action" to denote an improved and co-operative sort of effect, without necessarily qualifying it, in an attempt pre-empt some of the criticisms faced. 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 herbal mixtures, this may be very difficult to describe accurately as there are present constituents about which we know very little, either chemically, pharmacologically or even quantitatively. Antagonism is a much easier concept to define, being a reduced effect from that expected, and tends to be more easily demonstrated regardless of the mathematical derivation. To briefly summarise the measurement of synergy, the definitions of Berenbaum (1989) 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), 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 in 1940, (*via* Berenbaum 1989), and says that synergy is deemed present if the effect of a combination is greater than that of each of the individual agents – i.e. 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. It is however 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. An isobole is an "iso-effect" curve, in which a combination of constituents (da,db) is represented 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 occurring, i.e. the effect of the combination is greater than expected from their individual dose-response curves, the dose of the combination needed to produce the same effect will be less than for the sum of the individual components and the curve is said to be 'concave'. The opposite applies for antagonism, in which the dose of the combination is greater than expected, and produces a 'convex' isobole (Fig 1). 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.

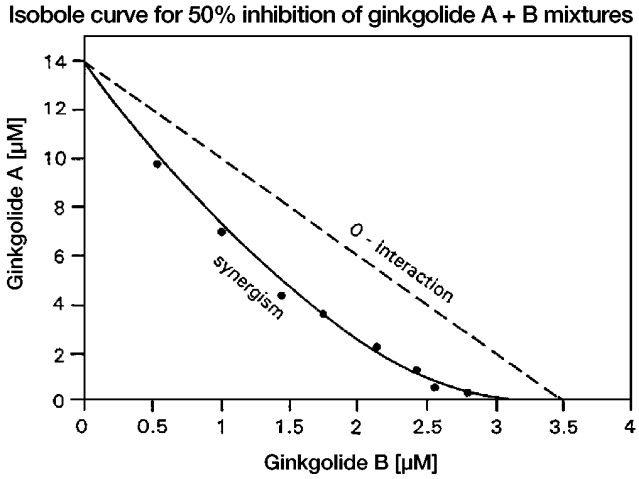


**Fig. 2.** Synergy between ginkgolides A and B measured using a platelet aggregation test.*

* B Steinke. Chemisch-analytische und Pharmakologische Untersuchungen von Pflanzlichen PAF-Antagonisten und Inhibitoren der Thrombozytenaggregation. Thesis, University of Munich (with permission) (see also Wagner, 1999).

The $IC_{50}$** values of various Ginkgolide A + B mixtures obtained by an *in vitro* induced platelet aggregation test.

| mixture GA:GB | $IC_{50}$ | quantity Ginkgolide A (GA) | | quantity Ginkgolide B (GB) | |
|---|---|---|---|---|---|
| | (µg/ml) | (µg/ml) | (µM) | (µg/ml) | (µM) |
| 3:1 | 2.40 | 1.80 | 4.41 | 0.60 | 1.42 |
| 2:1 | 2.20 | 1.47 | 3.60 | 0.73 | 1.72 |
| 1:1 | 1.80 | 0.90 | 2.21 | 0.90 | 2.12 |
| 1:2 | 1.55 | 0.52 | 1.27 | 1.03 | 2.43 |
| 1:3 | 1.40 | 0.36 | 0.88 | 1.09 | 2.57 |
| 1:10 | 1.30 | 0.12 | 0.29 | 1.18 | 2.79 |

n = 2–9

** $IC_{50}$ is the concentration causing a 50% inhibition of the platelet aggregation induced by PAF (platelet activating factor).

It is still routine practice 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 previously noted cytotoxic effect (Houghton, 2000). Only clinical trials can dispel these misconceptions, but they are expensive. Instead the effect should be anticipated, 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 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-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 include: valerian, *Valeriana* spp.; garlic, *Allium sativum*; ginger, *Zingiber officinalis*; hops, *Humulus lupulus*.
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 spez., 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.

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

## *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 for 50 % inhibition of Ginkgolide A/B mixtures (Fig 2). The presence of the other ginkgolides and the ginkgoflavones is also likely to have an affect on the overall activity and 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. 1987). However a dose of 120mg of a standardized Ginkgo extract containing only 6–7mg of ginkgolides, together with bilobalide and flavonol glycosides, has an equivalent 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 more effective when used as part of the extract, i.e. the "herbal shotgun" approach is vindicated here.

### Kava-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 herbal medicine for the treatment of mild anxiety states as an alternative to the benzodiazepines (Schultz et al. 1998). The chemical composition of kava 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. For details of these experiments see Singh and Blumenthal (1997).

### Liquorice, *Glycyrrhiza glabra*

Liquorice provides a number of examples of synergism between its own constituents, as well as with other herbs. It has been shown to affect absorption from the gut in an experiment where blood levels of glycyrrhizin were found to be lower, due to reduced absorption, when taken as part of an extract rather than as an isolated compound (Cantelli-Forti et al. 1994). A 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 as useful role in detoxification and suggests further investigation would be rewarding.

### Marihuana, *Cannabis sativa*

Recent research is confirming the role of cannabis 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

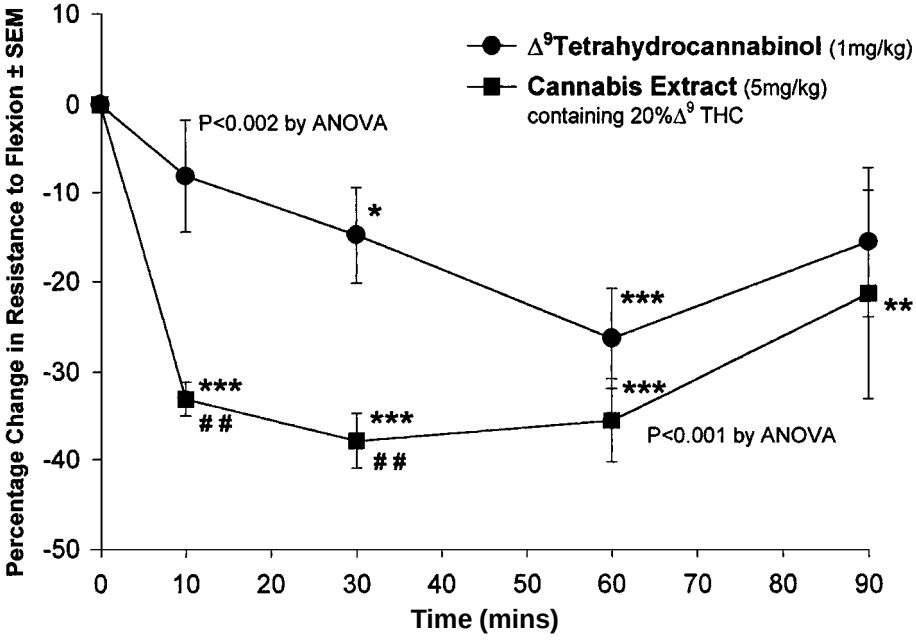


**Fig. 3.** Cannabis extract is a better antispastic agent than tetrahydrocannabinol at an equivalent dose (D. Baker and E. Williamson with permission).
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ compared to baseline (paired *t* test); ## $P < 0.01$ compared to % inhibition in $\Delta^9$THC-treated mice (*t*-test); Results represent recordings from 8 animals 12 limbs were analysed per group (Baker et al., 2000).

which can be attenuated by the presence of cannabidiol (CBD) in the herb, and patients of multiple sclerosis (MS) seem to prefer the herb to the isolated constituents for relaxant activity (Williamson and Evans 2000). There is additional evidence to show that the effect of the herb is both qualitatively and quantitatively different to isolated THC. The herb extract is a better antispastic agent than THC alone, as measured in an immunogenic model of multiple sclerosis (Fig 3), and has an effect on anandamide transport through membranes which is not shown at all by THC (unpublished observations). This synergistic effect will become very important if cannabis becomes a medicine by reducing the often undesirable psychotropic side effects.

### 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 (Hölzl 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. In an *in vitro* antimalarial test, the activity of artemisinin was enhanced by the presence of the flavonoids artemetin and casticin (Phillipson 1999). In another test, 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 not having this effect was naringenin and hesperetin, which may be explained by the fact that they are chemically very similar in that both are flavanones and differ only in a methoxyl group (So et al. 1996).

### Essential oils

Ginger, *Zingiber officinalis*, has been used 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 α-zingiberene, β-sesquiphellandrene, bisabolene and curcumene. Despite the fact that this fraction accounted for only a small proportion of the total, the effect 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 family contain essential oil and other components with antioxidant activity, and several of these are inhibitors of cholinesterase. 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 (Beukelman et al. 1995).

A mechanism by which monoterpene components of essential oils may interact with other drugs was accidentally uncovered during insecticidal testing of essential oils, where lethality on human lice was measured. 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 initially by looking at GABA-ergic activity, a mechanism through 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 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 5α-reductase and aromatase more significantly than the sum of either alone (Hartmann *et al* 1996). Experimental evidence of interaction between herbs was also provided by investigations into a clinically successful formulation of Chinese herbs used to treat eczema (Sheehan and Atherton 1992). When investigated both phytochemically and pharmacologically, activity was lost during fractionation (Phillipson 1999). The evaluation of synergistic effects for most of the Chinese herb formulations consisting of up to seven or more herb drugs, is complicated by the fact that the concept of treatment in Chinese medicine differs in many respects from that of western medicine.

## Clinical evidence

### Willow Bark

A randomised, placebo-controlled trial of the efficacy of a standardised extract of willow bark, *Salix alba*, for osteo-arthritis of the hip and knee, was carried out re-

cently. The study, in mainly elderly patients, was carried out in a hospital environment and measurement of pain assessed by both the patient and physician. The efficacy was confirmed, but the results went beyond that and synergy was implicated. Interestingly, the gastrointestinal side effects commonly encountered with nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin were not seen at the doses used, although it is usually assumed that willow bark is effective due to its salicin content. Salicin is a salicylalcohol derivative, which exhibits antiinflammatory and analgesic effects after transformation into salicylic acid in the liver. In the case of willow bark a lot of other salicylalcohol derivatives, flavonoids and tannins may contribute to this synergistic effect. However, when the amount of salicin in the study preparation was taken into account, the dose used (equivalent to 240mg salicin daily) was insufficient to explain the activity (Schmidt et al. 2001). Further investigations in the lab were then carried out, to see if another mechanism might be operating. Initially, the effect on the enzyme COX-1 (a cyclooxygenase) was examined but found not to be affected, despite the fact that it is inhibited by aspirin and is responsible for many of the side effects, especially those on the digestive system. However, COX-2, and lipoxygenase, which are involved in pain and inflammation were both inhibited (Heide, personal communication). This study shows that phytomedicines do not necessarily work in the same way as isolated constituents, and indicates that synergism may be taking place. It also implies that willow bark may be suitable for some patients for whom many NSAIDs would not be acceptable although if patients take very large quantities of the bark, aspirin-like effects are in fact still encountered.

### St John's Wort, Hypericum

The best methods for verifying the hypothesis of synergistic effects of constituents within a phytomedicine are controlled clinical trials performed with the standardized herb extract, on the basis of the concentration of bioactive constituents, and comparing it to synthetic drugs for the same indication. Up until the year 2000, at least 30 controlled clinical trials using standardized Hypericum extracts for mild to moderate depression have been carried out; of these, 12 trials were conducted against synthetic antidepressants (Schultz et al. 2000). No significant differences in efficacy were found between treatment with Hypericum extract and with synthetic antidepressants including imipramine, amitriptyline, maprotiline and fluoxetine; all resulted in the same reduction of depression score values. The ratio of Hypericum extract used, 500 mg/day, which corresponds to 8–10 mg bioactive constituents (hypericin, hyperforin, flavonoids, and procyanidins) was compared to imipramine at 150 mg/day (Woelk, 2000). The conclusion was therefore that a bioequivalence of 500 mg Hypericum extract with 150 mg imipramine indicates synergistic effects of the Hypericum constituents.

### Valerian and Kava-Kava

A combination of kava, *Piper methysticum*, and valerian, *Valeriana officinalis*, appears to be superior for the treatment of stress-induced insomnia than either herb alone (Wheatley 2001). This study was a small, open, cross over trial, 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 for getting to sleep, the hours slept and mood on waking. Initially, 24 patients were treated with a kava extract (LI-150) for six weeks, with a two-week washout. Nineteen patients then continued the trial with the valerian extract (LI-156) alone for another six weeks, followed again by a two-week washout. Finally these patients were given a combined preparation for six weeks. Stress was relieved by both preparations with no significant difference between them; however, the combination was significantly better ($P < 0.05$) especially for insomnia. Side effects were low, and consisted of either vivid dreams experienced with the combination and valerian or dizziness with kava-kava. Although the results are preliminary in nature, they certainly suggest that synergism between the two preparations was taking place. Another so-called fixed combination, consisting of the herbs valerian and hops, was officially accepted in a monograph by the German commission E because some studies have shown a mixture of 40 mg extract of hop and 60 mg Valerian-extract being bioequivalent with 400 mg Valerian extract alone.

### Ginseng and Ginkgo

In a double-blind, crossover trial using 20 young, healthy volunteers, a product containing ginseng, *Panax ginseng*, extract (GK-501,) with ginkgo extract (GK-511), was recently demonstrated to be more effective in improving cognitive function than either alone, as measured by the performance in various arithmetic tasks. Three studies were carried out using different doses of the extracts, and cognitive performance measured using "Serial Threes" or "Serial Sevens", which are tests involving subtracting from a random number. There was a seven-day washout between regimes. The single treatments showed improvements in line with previous findings, in that ginkgo extract improved speed and ginseng improved accuracy with the tests, however the combination produced a significant and sustained improvement in both aspects, and especially in the "Serial Sevens" test (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, at least a scientifically based explanation for the clinical bioequivalence of many plant extracts with synthetic drugs at the same therapeutic indications. A recent article in "New Scientist" examined the area recently and came to the conclusions: "To market herbal derivatives with full patent protection, they would have to do clinical trials on the active ingredients, separately and together. Compared with testing a single magic bullet, this is prohibitively expensive" and "without the support of the pharmaceuticals industry, herbs are likely to remain mired in uncertainty. What a waste." (MacKenzie 2001)

This sums up the problem neatly and economically. We now have an opportunity through further testing to prove that it is a true phenomenon, to be appreciated and utilised for therapeutic benefits.

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