NERVOUS SYSTEM

SCOPE
Apart from their use to provide non-specific support for recuperation and repair, specific phytotherapeutic strategies include the following.

Treatment in some circumstances of:
- stress symptoms;
- psychosomatic conditions;
- anxiety states, panic attacks;
- neuralgia;
- nervous exhaustion;
- insomnia;
- visceral spasm.

Management of:
- herpes infections;
- moderate visceral pain;
- mild to moderate depressive conditions;
- nervous debility;
- dose reduction for prescription hypnotics and sedatives.

As with any pharmacological agent, particular caution is necessary in applying phytotherapy in cases of:
- severe psychosis;
- prescription of powerful antipsychotics, antiepileptics, anaesthetics;
- addictive personality

ORIENTATION
Receptor activity
Although herbal remedies are not exactly comparable to conventional drugs in terms of directness of action, it is most likely that the primary effect of plant constituents on the nervous system is similarly on the synaptic junctions between nerve and nerve and nerve and muscle or other tissue. The receptor sites involved, whether on the presynaptic or postsynaptic membranes, are the communication junctions in the nervous system where its modulation is generally effected. The transmitter chemicals involved are among the most powerful molecules in the body and play a major part in the functions of other body systems; as seen in the relevant chapters of this book, plant constituents have been widely shown to engage with receptors in the hormonal, immunological and other control systems in the body. These systems form a whole whose study, psychoneuroimmunology, has attracted the attention of the more imaginative medical researchers since the 1960s. The ability of plant constituents to engage cell receptors is also a particular feature of activity within the digestive system (see p.163), which in clinical reality is probably the most accessible interface to the chemical control of the nervous system for herbal remedies.

There are ample opportunities for herbal constituents to interact with synaptic function in the nervous system. Various herbal extracts have been shown in vitro to act on adrenergic, muscarinic, 5-HT1A and 5-HT2 receptors, dopamine (D1 and D2), the benzodiazepine and the gamma-amino-n-butyric acid (GABA) binding sites.12 Particular examples of such activity follow; apart from familiar Western plants, much of the literature cited reflects the fact that most published research in this area emanates from China and Japan. While these experimental examples might not always reflect real clinical effects, they are given here to reflect the wide spectrum of possible activities of herbal remedies.

Calcium channel activity
Modifications of the movement of calcium ions through channels in the cell wall is a common factor in many receptor mechanisms. As well as the calcium channel-blocking effect of opioid alkaloids like protopine and tetrandrene (and see the Analgesic section below), this has also been observed in vascular tissues for ginseng saponins. A coumarin, scoparone, from Capillaris also inhibits calcium influx. From the Chinese remedy Dictamnus dasycarpus, calcium channel block was found with fraxinellone and dictamine, two constituents with vasorelaxant effect.

Adrenergic effects
The adrenergic effects of alkaloids of Ephedra, ephedrine and pseudoephedrine have been understood for many years. Beta-2-adrenergic receptor stimulation has also been mooted to explain the effect of Angelica sinensis in reducing experimental pulmonary hypertension;6 Rehmannia and Plastrum testudinis have also shown such activity in vitro.9 The nociceptive effect of processed aconite was demonstrated as involving adrenergic rather than opioid receptors10 and hypaconitine appears to be the most active of the alkaloids.11 The bronchorelaxant (antiasthmatic) effect of coumarins in the fruit of Cnidium monnieri is mediated by a beta-2-receptor and blocked by propranolol.12 Alismol, a sesquiterpenoid from Alisma orientale, demonstrated in vitro inhibition of noradrenaline release at adrenergic postsynaptic membranes.
Acetylcholine receptors

Acetylcholine is a common synaptic transmitter in the body. Acetylcholine-sensitive or ‘cholinergic’ receptors are divided into many types, depending on their other sensitivities. ‘Nicotinic’ receptors are also sensitive to the alkaloid from Nicotiana tabacum (tobacco). ‘Muscarinic’ receptors are also sensitive to muscarine from the fly agaric mushroom. The atropine-like alkaloids in plants of the Solanaceae (such as deadly nightshade, henbane and jimson weed) block muscarinic receptors in the parasympathetic nervous system. The effect of dried orange peel on digestive activity was blocked by atropine, suggesting activity on the muscarinic receptors. The traditional analgesic effect of Atractylodes lancea in cases of muscle pain has led to the isolation of an alcohol, beta-eudesmol, which has been shown to block muscle nicotinic receptors in vitro; this may be linked to an observed presynaptic depression of the regenerative release of acetylcholine in neuromuscular junctions. An action on the presynaptic membrane calcium channels to facilitate acetylcholine release at motor neuron terminals, apparently for the first time, is demonstrated for a lectin fraction of Pinellia ternata. Pinellia was also shown to stimulate vagal and thus gastric activity in vivo, an activity antagonized by apomorphine.

GABA and benzodiazepine receptors

The benzodiazepine valium was named in recognition of recent research that had established valerian as manifesting some tranquilizing properties. Although there are no chemical similarities between valerian constituents and benzodiazepines, some pharmacological similarities have emerged, with evidence that like the benzodiazepines, valerian acts in part through an action on the receptors on inhibitory neurons sensitive to gamma-amino butyric acid (GABA) (see also p.163). GABA-A and benzodiazepine receptor binding has been shown as a feature of a number of herbal remedies. For example, Salvia miltiorrhiza (dan shen), much researched in Beijing as a postulated treatment for ischaemic damage after strokes, and in the repair of other nerve tissue damage, has effects which apparently include stimulating GABA release and blocking calcium input. GABA secretion is depressed by a lactone fraction from Coriaria spp. Dipsacus saponin C has experimental antinociceptive effects; GABA-A, N-methyl-D-aspartic acid (NMDA) and non-NMDA receptors, but not opioid and GABA-B receptors, appeared to be involved in this activity.

Dopaminergic receptors

Tetrahydrocolumbamine from Poligala tenuifolia inhibits dopamine receptors, in part competitively, as does tetrahydropalmatine from Corydalis (and see below). In the monograph on chaste tree on p.328, other evidence for dopaminergic receptor activity is outlined.

Analgesic activity

Analgesics present a major challenge to the modern herbalist. Painkillers are by definition relatively powerful agents. Natural analgesics are likely to have been identified early in human history for their immediate benefits in pain relief and/or for their psychoactive properties. Obvious examples are the opium poppy (morphine alkaloids), the nightshade family (atropine alkaloids), willow, poplar and birch barks among other sources of salicylates and phenols, as well as the many psychoactive plants (coca, cannabis, psilocybin, mescaline, etc.). Most are now only legally prescribable by doctors, if at all, and it would appear that there is little scope for relatively gentle remedies to compete with the improved targeting of synthetic analgesics.

There are, however, a number of traditional remedies with general and specific analgesic reputations that have been less well exploited in modern times and which are relatively well tolerated in clinical use. Although not as powerful as some of the modern synthetic analgesics, they do show sufficient activity to be taken seriously and are particularly likely to be helpful in pain linked to inflammation and to visceral and vascular spasm. The research papers cited in the following examples demonstrate that even in the demanding area of analgesia there is ample evidence to support useful clinical intervention by the medical herbalist. Nevertheless, none of the following remedies are safe for widespread use by the public; their use is to be confined to the most experienced practitioner who can take account of all factors, including the increased likelihood of adverse effects.

Eschscholtzia californica (Californian poppy)

A traditional medicinal plant of the Indians, now used mainly by the rural population of western USA for its mild analgesic and sedative properties (and as the state flower of California). In studies on a prescription drug in Germany, Phytonoxon N containing E. californica and Corydalis cava (see below) at 4:1 relative concentration, investigators have identified interactions with opioid receptors, as well as other...
neurotransmitter activity. Aqueous-alcoholic extracts from *E. californica* also were shown to inhibit the enzymatic degradation of catecholamines as well as the synthesis of adrenaline, dopamine beta-hydroxylase and monoamine oxidase (MAO-B).

One separate study of the effects of the aqueous extract of the plant shows that at 25 mg/kg it had an anxiolytic action when administered intraperitoneally in mice, as measured by changes in behavioural parameters; at higher levels the effect became more sedative.

A key alkaloidal constituent, chelerythrine, is a well-known protein kinase C inhibitor with antitumour activity. Activation of protein kinase C in spinal cord dorsal horn neurons contributes to persistent pain following noxious thermal and chemical stimulation; chelerythrine produced significant reductions of nociceptive responses in one study. Another Canadian study suggests that chelerythrine can attenuate the development of morphine dependence. It demonstrates a range of effects on protein phosphorylation in different tissues and also demonstrates a range of potent antiinflammatory activities.

Chelerythrine and another alkaloidal constituent, sanguinarine, exhibited affinity for rat liver vasopressin V1 receptors and are competitive inhibitors of [3H]-vasopressin binding. These alkaloids represent two of the first non-peptidic structures providing original chemical leads for the design of synthetic vasopressin compounds.

*Corydalis cava et spp (yan hu suo)*

This remedy has been widely used in China and the East for pain, especially of dysmenorrhoea and the abdomen. In the studies on Phytonoxon N referred to above for *E. californica*, *Corydalis cava* was generally the stronger of the two ingredients.

Whole Corydalis extract demonstrated antispasmodic activity in acetylcholine-induced contractions at around half that seen for papaverine. Alkaloidal constituents have shown a range of activities. Isoisocoryne, like other phthalide isoquinoline alkaloids, produced an inhibitory effect on GABA-activated currents. Cavidine, protopine, corlumine, yehusomine and dehydroevodiamine have exhibited spasmodic activity. Dehydrocorydaline appears to block noradrenaline release and an experimental antiuclerative action is posited. Intravenous tetrahydropalmatine induces hypotension and bradycardia in rats and acts, apparently through 5-HT and/or D2 receptor antagonism in the hypothalamus, at levels comparable to one-tenth the dose of haloperidol. It also has powerful antiinflammatory effects. Tetrahydroberberine inhibited the rabbit platelet aggregation triggered by arachidonic acid and an inhibition of venous thrombosis in vivo. Various tetrahydropicrotobberine alkaloids have been shown to be selective alpha-1-adrenoceptor antagonists in vascular smooth muscle. Protopine isolated from Corydalis inhibited norepinephrine-induced tonic contraction in rat thoracic aorta in a concentration-dependent manner, probably by suppressing the calcium influx through both voltage- and receptor-operated calcium channels.

Traditional vinegar-processed preparations of the fresh Corydalis tuber have been shown to have stronger analgesic effects in vivo than those of the dried preparation. There appeared to be higher concentrations of total alkaloids in the fresh specimen.

*Evodia rutaecarpa (wu zhu yu)*

This remedy was traditionally used for pain, especially arising from abdominal and digestive causes with headaches and abdominal pain, including dysmenorrhoea. Evodia extract at various concentrations showed biphasic effects on the secretion of interleukin-1-beta, interleukin-6, tumour necrosis factor alpha, and granulocyte-macrophage colony stimulating factor by mononuclear cells in vitro. The effect was more stimulating at lower doses.

At least some of the effectiveness of Evodia has been linked to the fraction containing Evodiamine and rutaecarpine. A cholinergic mechanism has been implicated in this activity on the other hand, in the case of Evodia's vasodilatory activity, an alpha-adrenoceptor blocking and 5-HT antagonizing action are suggested, as well as for the powerful cardiotonic and uterotonic evodiamine and for the vasorelaxant and hypotensive dehydroevodiamine. This has itself demonstrated multiple receptor activities. Direct action on muscarinic receptors has been linked to its antiarrhhoal effect.

However, other antiinflammatory fractions have also been identified; antihistaminic and antinociceptive effects were reported for methanolic extracts of various Evodia species, though this was not directly correlated with alkaloidal content as such.

Among a number of plants tested Evodia showed a strong inhibitory effect on acetylcholinesterase in vitro and an antiscopolamine effect in vivo. This antiamnesic effect was more potent than that of tacrine which is the only drug for Alzheimer's disease approved by the FDA. The active component was identified as dehydroevodiamine hydrochloride.
**Stephania tetrandra (han fang ji)**

This Chinese medicinal herb has been used traditionally as a remedy for neuralgia and arthritis, especially febrile rheumatic disease, but its use in modern times is complicated by the apparently frequent substitution by Aristolochia. Tetrandrine, a key constituent alkaloid, has more recently been used to treat hypertension.

The vasodilatory action of tetrandrine is associated with in vitro observations of direct calcium channel block in vascular smooth muscle cells, lymphocytes, cardiac cells, rat glioma cells and bovine chromaffin cells. In vivo investigations demonstrate that tetrandrine inhibits KCl-induced intracellular calcium flow; it also inhibits norepinephrine-induced vasoconstriction in the presence of extracellular calcium. Findings suggest that tetrandrine is a structurally unique natural product calcium entry blocker. Hypotensive activity for tetrandrine has also been supported in experimental studies. Tetrandrine has been used in China as a treatment for silicosis, and antasilicosis benefits have figured largely in Chinese research. Its mechanism is unclear but it has been found to scavenge superoxide (O2·-) radicals produced from xanthine/xanthine oxidase, and has inhibited lipid peroxidation.

Bisbenzylisoquinoline alkaloids are known to affect immune as well as inflammatory responses and have been used for the treatment of inflammatory symptoms in China. In a study aimed at elucidating the inhibitory effects of two alkaloids, fangchinoline and isotetrandrine inhibited inflammatory mediators including cytokines and IL-1-beta.

Another constituent, tetrahydropalmatine, has analgesic, sedative and tranquillizing effects, involving dopamine receptor antagonist and depleting activity.

**Herbal sedatives and hypnotics**

In conventional pharmacological terms, sedatives reduce nervous activity and hypnotics promote sleep. There is obviously overlap in practice between the two categories, and both imply a degree of depression of nervous activity and consequent dangers (as seen most obviously in the barbiturates). There is a third category of calming agent that was postulated as an ideal anxiolytic strategy: the tranquilizer. This was originally defined as a treatment whose effect was confined to the reticular activating system that determined the level of arousal in the central nervous system, and did not otherwise sedate. Although the benzodiazepines were hailed as tranquilizers on their discovery, this ideal has been clearly compromised and these remedies are now seen to have appreciable sedative and hypnotic effects as well.

Many traditional herbal remedies have various degrees of sedative and tranquillizing activity and some have had this effect supported in experimental and clinical studies. However, it is probably misleading to apply the strict pharmacological definitions to them; their effects are much broader in clinical experience, with strong sedation rare. For the purposes of this text, therefore, the terms ‘herbal sedatives and hypnotics’ will be used to describe remedies that are actually relaxing, with little evidence of depressive activity. This herbal dimension is even more obvious in the next category.

**Relaxants and antispasmodics**

Most medical preoccupation has been with the nervous system as an entity in itself, with the goals of better analgesics, sedatives, tranquillizers and antipsychotics. Traditional interest in such areas was of course also strong and many plants were favoured for their powerful psychoactive properties. However, probably the most widespread use of nootropic plants, or nervines, nowadays is for their effects on innervated structures rather than on nervous tissue alone.

The antispasmodic (or spasmolytic) is a modern descriptor of the effect of an agent on visceral muscle in vitro, often the isolated guinea pig ileum. The technique is widely used as a model to indicate muscarinic or related receptor activity as above, but is a property with little therapeutic application. By contrast, herbal antispasmodics, spasmylytics or relaxants are remedies used to reduce the symptoms of tension in the body. Pre-Cartesian insights into the human condition had no separation between body and mind and this particular holistic view is a constant feature of Asian medicine still. Apart from the obvious psychoactives, remedies were not seen to be acting on the nervous system as such; rather there were many remedies that treated various manifestations of turbulence in the body linked to what nowadays would be described as ‘stress-related’ conditions.

Even though using other terms, early texts described such conditions as classic hypertension (‘Liver qi rising’), nervous headaches, palpitations, breathless attacks and hyperventilation (‘constriction of the chest’), nervous dyspepsia, dysphagia, irritable bowel and urinary frequency.

The remedies selected for these conditions were seen as somatic in emphasis. The markers for application and effectiveness were physical symptoms. Nowadays modern herbalists refer to many of them as antispasmodics or spasmylytics or, more recently,
‘visceral relaxants’. They are offered to the modern stressed patient as a welcome antidote to the culture of tranquillizers and sedatives, treatments working from the ‘neck down’ to reduce the physical effects of tension without befuddling the brain or impugning their sanity. Western remedies like those listed later have all developed reputations as useful management measures in helping patients handle and even overcome psychosomatic disorders, perhaps combined with appropriate breathing exercises and adrenaline-reducing aerobic activity. Some Chinese remedies like Uncaria rhynchophylla were targeted at such conditions and hold out the promise of modern applications.

PHYTOTHERAPEUTICS

Nervine tonics and nervous trophorestoratives

Herbal medicine has had to adapt significantly from its traditional roots. There is evidence that in many earlier cultures there were different perspectives on anxiety and tension syndromes. Whether there was genuinely less opportunity for the modern diagnosis in highly structured communities living on the edge of survival or whether such symptoms were not recognized as such is arguable. There is, however, less emphasis on treatments to relieve stress conditions in most traditional texts. There were also no powerful synthetic agents that relieved pain and distress. It is thus an entirely modern notion that herbs could provide gentle back-up for sufferers with nervous or mental problems.

In the West, where such adjustments have been made over many decades, the group of remedies that has emerged to meet modern needs is sometimes referred to as ‘nervines’. In recognition of the common observation that many conditions of tension are linked with fatigue, debility and depression, there is also a category of remedies that were seen to restore energies and build up strength. These have sometimes been referred to as ‘trophorestoratives’. It was a general principle that some tonifying element be included in most nervine prescriptions, so as to aim for lasting value rather than just short-term alleviation.

ANALGESICS

Plant remedies traditionally used as analgesics

Corydalis spp (yan hu suo), Eschscholtzia californica (California poppy), Evodia rutaecarpa (wu zhu yu), Gelsemium sempervirens (yellow jasmine), Paederia scandens (ji shi teng), Schefflera arboricola (qi ye lian), Stephania tetrandra (han fang ji). Topically: Bryonia alba (white bryony).

Indications for herbal analgesics

- Pain associated with inflammation (e.g. arthritis, chondritis, tendinitis, myalgia)
- Pain associated with visceral spasm (e.g. gallbladder, urinary and intestinal colic)
- Pain associated with vascular spasm (e.g. migraine, spasmodic dysmenorrhea)
- Neuralgic pain (in limited cases)

Other traditional indications for analgesics

- Primitive anaesthesia

Contraindications for herbal analgesics

As powerful agents, herbal analgesics should be restricted in their application to experienced and well-trained practitioners only. There is a theoretically increased risk of neurotoxicity and other adverse effects (although little known incidence) and there is always the possibility that individual examples could be withdrawn from use by regulatory authorities; this is most likely after cases of irresponsible use. The following cases should be approached with particular caution.

- Concurrent prescription of powerful analgesics
- Pain in children
- Neurological disease
- Depression and psychosis
- Liver and kidney disease
- History of allergic or anaphylactic reactions

Application

Herbal analgesics may be taken as required or before food. There is likely to be a longer delay compared with synthetic analgesics and the temptation to dose excessively must be resisted.

Long-term therapy with analgesics is not advisable.

Advanced phytotherapeutics

Herbal analgesics may also be usefully applied in some cases (depending on other factors) of inflammatory disease.

HERBAL SEDATIVES AND HYPNOTICS

Plant remedies traditionally used as sedatives and hypnotics

Corydalis spp (yan hu suo), Humulus lupulus (hops), Lactuca virosa (wild lettuce), Passiflora incarnata (passionflower), Piper methysticum (kava), Piscidia
**Herbal approaches to system dysfunctions**

*Herbal sedatives and hypnotics*

- Moderate tension and anxiety syndromes (short-term or intermittent use)
- Insomnia (difficulty in getting off to sleep first thing at night)
- Weaning off conventional sedative prescriptions

**Other traditional indications for sedative and hypnotics**

- Restlessness disturbing convalescence

**Contraindications for herbal sedatives and hypnotics**

As generally milder than prescribed sedatives, herbal equivalents should not be seen as immediate substitutes in the more serious indications. It would be unwise and even dangerous to drop the use of strong sedative medication without careful planning, preferably with the cooperation of the prescribing physician.

- Depression
- Insomnia marked by increasing restlessness during the early hours of the morning

**Traditional therapeutic insights into the use of sedatives and hypnotics**

In what were usually harsher and more robust times, the need for sedatives was often urgent, and opium extracts were the most favoured. The main tradition of use of moderate herbal sedatives were as short-term components of convalescent management, particularly to help with sleep. There was apparently little use of sedatives for wider lifestyle management.

**Application**

Herbal sedatives and hypnotics may be taken as required, at bedtime or before food.

Prescription of herbal sedatives should be limited. In the first place they are part of an essentially negative strategy that aims to substitute stupor for resolution of underlying problems. Although most unlikely to lead to addiction, compared with modern sedatives, the body may habituate to herbal sedatives and hypnotics with diminishing benefits.

**Advanced phytotherapeutics**

Herbal sedatives and hypnotics may also be usefully applied in some cases (depending on other factors) of inflammatory disease.

**ANTISPASMODICS AND RELAXANTS**

*Plant remedies traditionally used as antispasmodics and relaxants*


**Indications for antispasmodics and relaxants**

- Anxiety, irritability and restlessness, including in children
- Sleeplessness due to anxiety and irritability
- Nervous dyspepsia
- Irritable bowel and intestinal colic
- Tension headaches and migraines
- Spasmodic dysmenorrhoea

**Contraindications for antispasmodics and relaxants**

As a group these remedies are generally safe and well tolerated.

**Traditional therapeutic insights into the use of antispasmodics and relaxants**

Early use of antispasmodics also appears to have been dominated by their emergency indications, notably urinary and biliary colic. The use of milder relaxant treatments was mainly as tisanes for children and in the largely unrecorded but vast realm of family care. As expected, systematic classifications of medicine throughout history are generally silent on this area of popular healthcare.

Relaxants were obviously indicated for functional overactivities, indications like dyspeptic and colicky conditions were probably the most common (and carminatives like the spices the most frequent tisanes). Headaches, teething and restlessness in children and menstrual pains were likely to make up most of the remaining indications. These were usually treated...
within the home by local remedies with recipes handed down through the family.

It remains true to this day that often the most effective relaxant therapy is a cup of hot herbal infusion.

Some remedies are more sedative than others in this class (see above). These might be added to a relaxant prescription to increase its impact. However, sedation may be deleterious: the more a remedy is chosen for its sedative effects, the shorter the treatment should be and the more tonifying remedies should be added (see following section). The latter should also be a major element in prescriptions for the increasing proportion of tension conditions linked with fatigue, debility, depression and exhaustion.

Application

Antispasmodics and relaxants (and also those aromatics and volatile antispasmodics used for this purpose) may be best taken as hot infusions, though the ordinary teabag may not be sufficiently strong compared with the traditional brew and in acute cases, traditional doses were very high indeed. However, the following herbs probably work better in aqueous ethanolic extracts: Dioscoria spp, Lobelia inflata, Passiflora incarnata, Piper methysticum, Valeriana officinalis, Viburnum opulus.

Long-term therapy is generally well tolerated and may be appropriate, although the use of more sedative remedies should be reduced.

NERVINE TONICS (NERVOUS TROPHORESTORATIVES)

Plant remedies traditionally used as trophorestoratives

Avena officinalis (oat straw), Hypericum perforatum (St John’s wort), Scutellaria lateriflora (skullcap), Turnera aphrodisiaca (damiana), Verbena officinalis ( vervain), Withania somniferum (Indian ginseng).

Indications for trophorestoratives

(see also Tonics, p.155).

- Nervous exhaustion
- Neuralgia, herpes infections
- Depressive states
- Insomnia (waking up in the small hours after getting off to sleep easily)

Other traditional indications for trophorestoratives

- Convalescence
- Neurasthenia

Contraindications for trophorestoratives

True trophorestoratives are almost nutritional in their effects, with few risks of adverse effects except in those patients with extremely debilitated constitutions (see also the discussion on tonics).

Traditional therapeutic insights into the use of trophorestoratives

Neurasthenia encompassed a wider range of disorders than nervous exhaustion. In days before psychoanalysis and neurology, it included symptoms where the nervous tissues were seen to be affected such as neuralgia and neuritis, depression, anxiety states and neurasthenia. The trophorestoratives were thus often combined with other tonics and convalescent foods such as molasses, yeast and malt extract (now known as rich sources of the B vitamins), oatmeal and other cereals.

Application

Trophorestoratives may be taken as required or before food.

Long-term therapy with trophorestoratives is generally the norm.

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Herbal approaches to system dysfunctions


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