MEDICINAL PLANTS IN AUSTRALIA

Volume 4 An Antipodean Apothecary

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Foreword

As botanists working in a national scientific research institution, my colleagues and I receive many queries from the general public. One of the most frequent areas of enquiry relates to the uses of Australian plants by humans, either for ornament, food or, more significantly, their toxic or medicinal qualities. The last subject has always been a difficult one to respond to, due to the dearth of recent, reliable information. Information on the medicinal properties of Australian plants does exist, but it is widely scattered throughout the scientific and popular literature and as such is not readily available.

At least that *was* the case, until Cheryll Williams embarked upon her ambitious and impressive series, *Medicinal Plants in Australia*. I first became aware of Cheryll and her work in 2008, when I received an enquiry from her regarding scientific name changes in the Myrtaceae. Thankfully this is an area in which I have some expertise (as opposed to medicinal plants, of which I am largely ignorant), and I was able to help. I also referred her to the Australian Plant Census (APC), a national, collaborative project managed on behalf of the Australian taxonomic botany community by my home institution, the Australian National Herbarium.

There began a fruitful and enjoyable relationship; I was impressed and pleased that Cheryll went to such effort to ensure accuracy in a subject (plant taxonomy and nomenclature) that many authors seem content to ignore. As Cheryll mentioned in the first volume of *Medicinal Plants in Australia*: 'It [plant taxonomy and nomenclature] is an extraordinarily complex subject … and can drive one to distraction'. I may not always have been able to answer her queries with absolute certainty, the fluid nature of taxonomy and differing opinions negating a definitive answer in some cases; nonetheless, for the most part I like to think I have helped prevent Cheryll from sliding into complete despair and despondency when wrestling with the concepts I and my fellow taxonomists are responsible for generating.

When the first volume appeared, I was amazed at the scope and depth of the information presented. My knowledge of medicinal plants is limited at best, and I had no idea of the number of species in the Australian flora which have known or suspected medicinal properties. I had initially thought that Cheryll was intending to publish a single, stand-alone volume, but I soon realised that there was far, far more to this subject than I had imagined.

Cheryll's careful research and collation of this otherwise scattered information makes for authoritative and entertaining reading. There is the danger that such works may lean too far towards a popular interpretation and sacrifice accuracy for readability, or alternatively tend towards overt and unnecessary detail. *Medicinal Plants in Australia* is neither of these. The information presented is clear, concise and (most importantly) *reliable*, referenced as it is to the large scientific literature on this subject and interpreted by someone who is an authority in the field.

Through regular email exchanges, I also became aware of the enormous amount of effort required to see each subsequent volume through to fruition and I found myself keenly anticipating the arrival of each new volume. However, in my case it was more a matter of pleasant satisfaction at seeing the finished work, as opposed to exhausted relief at having completed another huge undertaking! Even when struggling under the weight of proofreading, chasing obscure references or interpreting my responses to her queries(!), Cheryll manages an enviably cheerful outlook.

I always look forward to the snippets of news from her north Queensland home that often accompany a query or an update on the status of the next volume: newly hatched cassowary chicks in the backyard, three metres of rain falling in five minutes, flying foxes on the back verandah, all things quite foreign to someone in cool, dry Canberra!

Medicinal Plants in Australia is a work that sits prominently in the libraries of both the Australian National Herbarium and the Australian National Botanic Gardens here in Canberra; no doubt it has also found a place in many other libraries in Australia and overseas, as well as on the shelves of anyone interested in Australian plants. It is a work that speaks of the drive, determination and passionate interest of its author, and one that I am very pleased to have been involved with in some small way.

Brendan Lepschi
Curator, Australian National Herbarium
Canberra, 2013

Chapter 4

NEW ROLES FOR OLD REMEDIES

Australian native herbs have impressive healing attributes – although only a few have been exploited to their full potential. However, there are other traditions that indicate profound medicinal potential for some of these plants, or their close relatives, that have hitherto been largely ignored in this country. In many cases, the traditional use of numerous herbs has been verified by modern investigation, which serves to enhance their practical value. Some studies hint at greater healing attributes than is immediately apparent – as pharmacological evaluations of the Horsechestnut, Gotu Kola and Brahmi illustrate. Their benefits range from venous, tonic and wound-healing activity, to liver and kidney protective properties, as well as significant effects for memory enhancement.

Gotu Kola is one of the herbal remedies with particularly interesting antimicrobial attributes that once led to its extensive use as an antileprotic remedy – a disease that many of us mistakenly consider a remnant problem, relegated to historical significance. The reality of the situation is quite different. The story of leprosy, an intractable disease with disastrous consequences for the sufferer, involves a rather amazing search for wound-healing remedies and a complex tale of antibiotic discovery. Even so, the role for herbal medicines, somewhat surprisingly, remains as valid today as in the past.

Centella: Ancient Remedy for the Modern World

A Coastal Weed

Gotu Kola or Indian Pennywort (*Centella asiatica*, formerly *Hydrocotyle asiatica*) is a slender creeping plant of garden edges, shady stone walls

Gotu Kola.

and rockeries. It flourishes particularly well on damp swampy sites. The plant, which has also been known as Miner's Lettuce, favours the east Australian coast, ranging from Victoria to tropical Queensland – as well as a being found in a few places in South Australia and southwest Western Australia. Despite its impressive medicinal potential, *Centella asiatica* is often considered to be little more than a tropical weed. The botanical literature, with regard to the classification of *Centella* and *Hydrocotyle*, can be somewhat confusing. Some authorities regard *Hydrocotyle asiatica* and *H. cordifolia* as synonyms for *Centella asiatica* – although others regard them as separate species. These plants are virtually indistinguishable in appearance. In addition, Gotu Kola has sometimes been erroneously known as Brahmi – a term ascribed to *Bacopa monniera*.

It is a pity that many small herbs such

Gotu Kola as herbal lawn cover, no mowing required.

as *Hydrocotyle* and *Centella* are often seen as nuisance weeds. Surely some daisies, dandelions, oxalis, clovers and pennyworts could add an attractive diversity to the lawn environment, with the added benefit of a low growth habit and colourful flowers – although invasive imported weeds such as the Singapore Daisy (particularly in the rainforest environment) would be an exception. Certainly native species that can be utilised as natural lawn alternatives may be best left alone – rather than using expensive herbicides that poison the soil and add to chemical run-off in the urban setting.

Gotu Kola or Indian Pennywort (*Centella asiatica*) is native to India, China, Indonesia, Australia, the South Pacific Islands, Madagascar and southern/central Africa. Throughout its range it has been regarded as a wound-healing herb *par excellence*. The fresh plant (or its juice) has been utilised in the treatment of a great diversity of wounds that range from abscesses and ulceration (chronic, scrofulous, or syphilitic with gummatous infiltration) to innumerable skin problems (psoriasis, chronic or obstinate eczema, boils, furunculosis, sweat rash).

The entry for *Centella asiatica* in the 1868 *Pharmacopoeia of India* states: 'In anaesthetic leprosy good results have followed the use of this herb, but it possesses no claim to the character of a specific attributed to it by some. It has been found more useful in secondary or constitutional syphilis, especially in those cases where the skin and subjacent cellular tissue are principally affected. In non-specific ulcerations, and in skin diseases, it is of value, both as an internal and as a local remedy.'

An early report in the *Agricultural Gazette of New South Wales* made mention of an indigenous plant possessing medicinal properties (Maiden 1894):

> *[Hydrocotyle] asiatica* is found in moist places in many parts of the Colony. In the coast districts, and particularly near the northern rivers and table-lands where there is rich soil, it grows in the greatest profusion, covering the ground for large areas with a carpet of bright green … Mr. G. M. M'Keown, Manager of the Experimental Farm at Woollongbar, Richmond River, recently sent this plant to the Department, stating that it is 'credited locally as valuable when applied to wounds or sores in the form of a salve or poultice'. This is the first occasion on which I have heard of it being put to use in New South Wales, but it is a well-known remedy in India, having been in use amongst the natives for many centuries.

Brisbane doctors accorded it similar esteem and the herb even gained some official recognition. In 1888 Gotu Kola was an exhibit at the Melbourne Centennial International Exhibition.

The report in the *Agricultural Gazette* continued:

> The *Pharmacographica Indica* (1891) confirms the above estimate of the therapeutic value of the drug, and also states that it is so abundant in the Mauritius [Islands] that it serves as forage for cattle, whose milk it improves; it is also greedily eaten by pigs and other domestic animals. It is the more desirable to draw attention to an indigenous medicinal plant, as we have so few that, in the present state of our knowledge, possess undoubtedly valuable properties. In the bush it will be most convenient to employ the plant in the manner and for the uses indicated in Mr. M'Keown's note.

The Pennyworts

Centella (Apiaceae) was formerly placed in the genus *Hydrocotyle* – which belongs to a different family classification, the Araliaceae. Over half the *Hydrocotyle* genus is found in Australia (41 of a total of 75). These fairly attractive creeping herbs of marshy and boggy places are often known as Pennyworts, and have a somewhat similar appearance to Gotu Kola.

The Large-leaf Pennywort (*Hydrocotyle bonariensis*) is of interest as it is a medicinal herb that is widely distributed across the globe – from tropical and South Africa to the southern United

Hydrocotyle bonariensis. (Upper image courtesy Donald Hobern, flickr; lower image courtesy Franz Xaver, Wikimedia Commons, CC-by-SA 3.0 Unported)

States, Central and South America. In Australia it is found along the coastline from southern Queensland to Victoria, South Australia and Western Australia (southwest region). The plant has been utilised for treating inflammatory skin disorders including psoriasis, and as a cosmetic for freckles and skin spots. Extracts possess antifungal (fungicidal) activity against *Candida krusei*. This herb has also shown significant antiparasitic activity against *Leishmania amazonensis* (Tempone 2008).

The Whorled Pennywort (*Hydrocotyle verticillata*) is a native species found throughout southeastern Australia, ranging to inland Queensland and South Australia, as well as southwest Western Australia – although it does not extend to the northern tropics or Tasmania. This species is often utilised as an aquarium foliage plant. (Image courtesy Kim and Forest Starr, Hawaii)

The Lawn Marsh Pennywort (*Hydrocotyle sibthorpioides*) is prolific throughout Victoria and Tasmania, extending along the coastline of New South Wales into southern Queensland. This native species has shown substantial immune modulatory and anticancer potential. The aquarium herb known as Brazilian Pennywort (*Hydrocotyle leucocephala*) is also of interest due to its immunosuppressive components (Huang 2008; Yu 2007; Ramos 2006). (Image courtesy Kim & Forest Starr, Hawaii)

A Remarkable Therapeutic Repertoire

Investigations of *Centella asiatica* and its components confirm significant wound-healing attributes. The Gotu Kola herb can directly promote collagen synthesis, which is important because collagen is a major skin component that is directly involved in the healing process. The effects are linked to its triterpene components – the most prominent of which are asiaticoside and madecassoside, and their sapogenins (asiatic acid and madecassic acid). In the past, particular emphasis has been placed on the cellular healing and antimicrobial effects of asiaticoside, although madecassoside appears to have equally impressive activity (Paolino 2012; Somboonwong 2012; Belcaro 2011; Hashim 2011; Maquart 1999; Sunilkumar 1998; Suguna 1996; Bonte 1995, 1994, Rush 1993).

The effects of asiaticoside are multifaceted. It has substantial antioxidant and anti-inflammatory properties which facilitate the initial stages of healing.[1] It can increase the vascularisation of connective tissue, provide support for the tensile integrity of the skin, and facilitate keratinisation (keratin is a protein primarily found in skin, nails, hair, tooth enamel), which is involved in skin formation – thereby also having a stimulant effect on hair and nail growth (Turton 1993; Shukla 1999a, 1999b).

Importantly, not only does Gotu Kola promote skin repair, it also strengthens the cellular structure of the skin, maintaining its integrity. The use of the herb in the treatment of venous insufficiency, inflammation (phlebitis) and for ulceration of the extremities (e.g. leg ulcers) is not only based on a wound-healing effect – there is a supportive action on the venous circulation, with substantial anti-inflammatory benefits. Bed sores and diabetic ulcers, which likewise involve impaired circulatory function, respond well to treatment with Gotu Kola. It can promote the formation of new epithelial cells and connective tissue, allowing the damaged tissue to be discarded more quickly. Therefore, burns heal quicker with its use, and it can reduce keloid (scar) formation (Somboonwong 2012; Kimura 2008; Liu 2008b; *Altern Med Rev* 2007).

1 The antioxidant activity of *Centella asiatica* (84%) has been found comparable to that of grape seed extract (83%) and vitamin C (88%) (Hashim 2011).

Gotu Kola extracts have anti-inflammatory, anti-pruritic (anti-itching) and anti-allergic properties (George 2009). Serious investigation of its use as a topical treatment for psoriasis has been suggested (Sampson 2001). The anti-inflammatory and antioxidant triterpenes asiaticoside and madecassoside make a significant contribution to its anti-psoriatic properties. Gotu Kola also has potential for use in cellulitis – a diffuse inflammatory disorder characterised by localised hot red patches of skin irritation (e.g. erysipelas) that can become extensive. The condition can be extremely painful and debilitating (Morganti 1999; Kartnig 1988). In addition, experiments tend to confirm an immune-supportive effect (Punturee 2005a, 2005b, 2004; Jayathirtha & Mishra 2004). The use of *Centella* in individuals with compromised immune system function, particularly where circulatory impairment can delay wound healing (such as diabetes), is certainly justified.

A number of studies indicate Gotu Kola extracts can be useful following surgery. The herb has the ability to promote mucous membrane healing in ear, nose and throat surgery – for example, following tonsillectomy. It can enhance the healing process for all manner of surgical wounds (including episiotomy lacerations following childbirth) – as well as radiation-induced ulceration (Mowrey 1990). A cream combining *Centella asiatica* and *Bulbine frutescens* has been used clinically as a supportive healing agent following plastic surgery, specifically for the reduction of scar tissue formation. The cream not only promoted collagen production and facilitated wound healing, it had useful antibacterial and anti-inflammatory activity (Widgerow 2000).

Many products on the market that contain Gotu Kola are equally effective. Cream formulations combining Gotu Kola with *a*-tocopherol and collagen-elastin hydrolysates can prevent the stretch marks of pregnancy – a combination that was found to be particularly useful for women who had developed them previously (Young & Jewell 2000). Gotu Kola may help prevent skin ageing and wrinkles. The herb has photoprotective properties and a cream prepared with madecassoside and vitamin C showed substantial benefits for chronic sun-damaged (photoaged) skin (Saraf 2012; Haftek 2008). Research continues to improve the bioavailability of *Centella* formulations

A South African herb known as the Burn Jelly Plant (*Bulbine frutescens*) is well named. The fresh leaf yields a soothing mucilaginous juice with an excellent healing reputation that is particularly useful for burns – as well as all sorts of skin irritation (rashes, blisters, insect bites), cracked or fissured skin problems (lips, feet), acne, mouth ulcers and even cold sores (www.plantzafrica.com). (Image courtesy Stan Shebs, Wikimedia Commons, CC-by-SA 3.0 Unported)

Tagetes patula. (Courtesy Michael Lahanas, Scientific-web.com)

for more effective clinical use, including the development of titrated extracts of *Centella asiatica* (TECA), organogels and hydrogels (Belcaro 2011; Morales 2009; Hong 2005; Kim 2001).

A number of other remedies with good wound-healing and antibacterial attributes have equally interesting potential. For instance, 'Calendula ointment' has shown practical benefits for treating trophic ulcers such as those of leprosy. However, Kartikeyan and colleagues (1990) provide an illustration where checking the botanical identification is essential. Despite the name, the preparation used in the investigation was not based

Calendula officinalis. (Courtesy Fanghong, Wikimedia Commons Project, CC-by-SA 3.0 Unported)

on *Calendula officinalis* – instead it utilised a tincture of Marigold flowers from *Tagetes patula* with 10 per cent white paraffin. The results were very good: 'After 3–4 weeks, patients using calendula ointment showed 30–40% reduction in depth and diameter of the trophic ulcers and absence of any secondary infection, despite their refusal to immobilize the affected part.[2] Since calendula is a natural product with no known untoward effects we feel that our observations may be useful to field personnel facing similar problems' (Kartikeyan 1990). *Calendula officinalis* does have a similar effective reputation (Jorge-Neto 1996).

Circulatory and Cardiovascular Support

Gotu Kola has an excellent reputation for diverse conditions involving impairment of the venous system, such as haemorrhoids and varicose veins (MacKay 2001). In the last decade, investigations have greatly expanded its therapeutic scope. The benefits of the herb have long been known to traditional Indian and Chinese medical practitioners, although European interest lagged behind until the advent of studies undertaken in Italy in the 1990s (Cesarone 1994, 1992). Subsequently, greater recognition of the significant benefits of the herb by the medical profession resulted from clinical studies undertaken at St Mary's Hospital, Imperial College, London (Cesarone 2001a, 2001b, 2001e; De Sanctis 2001; Incandela 2001b, 2001c).

2 Immobilising the affected site was part of the treatment protocol as this helps to promote healing and prevent repeated trauma. Plaster casts, however, were considered stigmatising and not very practical as most patients needed to continue working. Antibiotics (neomycin) were the common method of ulcer treatment (Kartikeyan 1990).

Gotu Kola Tincture. (Courtesy Nutrition Care)

Studies on the use of a triterpene fraction for treating chronic venous insufficiency demonstrated a favourable influence on the circulatory status of diabetic individuals – as well as being useful for the treatment of venous hypertension. Although the initial clinical studies were small, the results were impressive. Importantly, the extract helped to prevent the deterioration of peripheral circulation that can be a seriously debilitating long-term consequence of diabetes. The herb also has potential for improving cardiovascular function, notably for the treatment of atherosclerosis. It can stabilise plaque formation and thereby reduce the risk of thrombosis. The fact that the extract can be used in conjunction with other drug therapies, and is very well tolerated, is a substantial therapeutic bonus (Cesarone 2001d; Incandela 2001a, 2001d).

The use of Gotu Kola for the prevention of thrombosis on long-distance travel is another point of interest. Clinically, use of a triterpene-rich extract showed a marked reduction in ankle swelling and oedema. There were practical benefits for individuals undertaking long-haul flights or road travel that could be particularly useful for preventing microcirculatory problems. Importantly, the extract was effective even when used on a short-term basis. The dose was fairly low – 60 mg three times daily for two days before, as well as during the flight, with its use being continued for the following day (Cesarone 2001c). Of course, for seriously compromised circulatory problems a more long-term strategy would be appropriate.

However, a word of caution is required regarding the use of herbal therapies that influence the circulatory system. Although they can provide substantial benefits, their use with blood-thinning drugs such as warfarin (the use of which can be a complicated undertaking at the best of times) requires careful monitoring. Even so, this does not preclude the use of supportive herbal therapies.

Centella's therapeutic potential appears to be best evaluated according to its chemical characteristics, with an emphasis on asiaticoside and madecassoside as the compounds of primary interest. This has been made somewhat easier with the development of a number of standardised triterpenoid-rich extracts (James & Dubery 2009):

- TECA (titrated extract): composed of asiatic acid (30%), madecassic acid (30%), asiaticosides[3] (40%)
- TTF (total triterpenoid fraction): composed of asiatic acid and madecassic acid (60%), asiaticosides (40%).
- Madecassol extract: asiaticoside (40%), asiatic acid (29–30%), madasiatic acid (1%).

There is another aspect of Gotu Kola's chemical complexity that is worthy of note. The main components of the terpenoid-rich essential oil are: *a*-humulene, *β*-caryophyllene, bicyclogermacrene, germacrene, myrcene, trans-*β*-farnesene, and *p*-cymol[4] (James & Dubery 2009). Certainly, some of these would exert an influence on the activity of the herb. In addition, various other components are present in plant extracts: an alkaloid (hydrocotylin), flavonoids (kaempferol, quercetin, rutin) and other phenolic compounds (catechin), sterols (stigmasterol, sitosterol), amino acids, resin and a bitter principle (vellarine).

The herb's use as a vegetable is certainly supported by its nutritional value: vitamins (vitamins B, C, carotenoids) and minerals (calcium, magnesium, phosphate, sulphate, sodium, potassium, chloride). Indeed, iron levels can be quite high (12 mg/100 g). There is also a reasonable calcium (176 mg/100 g) and carotene (2400 mcg/100 g) content (Jamil 2007). The carotenoids of interest include *β*-carotene (255 *μ*g/g dry weight), lutein (980 *μ*g), neoxanthin (103 *μ*g) and violaxanthin 9255 *μ*g) (Chandrika 2010).

3 There is more than one form of asiaticoside. In addition to the original compound, asiaticosides B, C, D, E and F have been identified.

4 Other studies have shown variations in the main components. A volatile oil with antidepressant activity contained farnesol, elemene and caryophyllene. Another analysis showed *a*-humulene, *β*-caryophyllene and bicyclogermacrene predominated (Zheng & Qin 2007).

A Complex Triterpenoid Chemistry

Centella asiatica.

There appears to be quite a deal of variability in the constituents of Gotu Kola plants obtained from different sources. The herb can contain a number of components that are very similar chemically. However, the older literature is confusing, with duplicate chemical names, synonyms and, at times, contradictory findings marring the clarity of the picture (James & Dubery 2009). For instance, one study stated brahmic acid was identical with madecassic acid, while isobrahmic acid was a mixture of asiatic and madecassic acids (Kartnig 1988). Yet another report stated isobrahmic acid was identical to madecassic acid (an isomer of terminolic acid). Currently brahmic acid and madecassic acid are considered to be the same (6-β-hydroxy-asiatic acid) (James & Dubery 2009).

For a long time Madagascar-sourced *Centella asiatica* was justifiably considered preferable as a wound-healing remedy due to its higher asiaticoside content. This was a fairly safe option, particularly as diverse studies reported considerable variability in plant extracts from other sources – a chemical complexity that would be, for most of us, quite bewildering. There are, however, varieties that maintain a great deal of similarity and the discovery of different chemical races of the herb has helped to clarify the situation (Kartnig 1988). The total triterpenoid content was, in general, found to be comparable between plants from India, Korea and Madagascar – although differences occurred in the ratio of free acids (e.g. asiatic acid) to glycosides (e.g. asiaticoside). Rosmarinic, betulinic and ursolic acids are additional compounds of pharmacological interest. Some species also contain saponins (e.g. centellasaponins A, B, C, D).

The standard reference is: asiaticoside (1 mg/ml), madecassoside (3 mg/ml) and asiatic acid (10 mg/ml) (Zainol 2008). Overall the following characterises plants obtained from different locations (James & Dubery 2009[5]):

- Madagascar: asiaticoside, asiatic acid, madecassoside and madecassic acid. Asiaticoside is present at high levels (2.6–6.42% dry weight) in the leaf. The roots contain negligible levels. Cultivated plants had a much lower saponin content (asiaticoside 0.7–0.9%, madecassoside 1.1–1.6% dry weight).
- South Africa: asiaticoside, asiatic acid, madecassoside and madecassic acid.
- Sri Lanka: centelloside, centellic acid (plus centic and centoic acids).
- Indian-sourced plants showed the greatest chemical variability (with different chemical types as listed):
  - ★asiaticoside, asiatic acid, madecassoside and madecassic acid (plus brahmic acid)
  - ★asiaticoside and asiatic acid
  - ★brahmoside and brahmic acid (plus isobrahmic acid)
  - ★brahminoside, brahmic acid (plus betulinic acid)
  - ★thankuniside, thankunic acid (plus asiatic acid)
  - ★isothakuniside and isothankunic acid (plus asiatic acid)
- Malaysian samples (mg/ml) were found to be low in asiatic and madecassic acids (0.55 ± 4.58 mg; 0.55 ± 0.89 mg, respectively), although the level of madecassoside (3.1 ± 4.58 mg) and asiaticoside (1.97 ± 2.65mg) were good (Hashim 2011).

5 A complete list of triterpenes and their chemical structures is available in James & Dubery (2009). Ursolic and betulinic acids are discussed in greater detail in Volume 2 under *Triterpene discoveries*.

- Southern Malaysian samples (mg/ml): asiaticoside (2.5 mg), madecassoside (5.3 mg), asiatic acid (3.4 mg) (Zainol 2003). Other leaf samples[6] have shown substantial variability (mcg/ml): asiaticoside (0.39–2.56 mcg), madecassoside (0.71–5.3 mcg), asiatic acid (undetectable–1142.67 mcg). Substantial levels of asiatic acid (2390 mcg) were also present in the petioles.
- Australian sources have similar potential for chemical variability. It is also possible that the native herb is not entirely botanically identical with overseas samples and may even be a different variety or sub-variety. At one time the native plant was assigned a separate species name, *Centella cordifolia.*

6 While root samples normally contain minimal amounts (if any) of these triterpenes, in this study levels of 3421 mcg/ml asiatic acid and 1.57 mcg/ml madecassoside were present.

A Neuroprotective Agent

Gotu Kola has been traditionally valued as a brain tonic and memory-protective herb – a reputation that has been supported by current research. The herb has antioxidant, anti-inflammatory and neuroprotective properties that affect brain function, with potential benefits for age-related memory loss and conditions such as Alzheimer's and Parkinson's diseases. It may even be useful for neurodegenerative disorders such as Huntington's disease and multiple sclerosis. The research effort regarding this area of the plant's potential has been impressive. Interestingly, some experiments have indicated that Gotu Kola can help the regeneration of nerve cells. Moreover, the herb has shown anti-epileptic (anti-convulsant) and anti-depressive potential that suggest its use as an adjunct for the treatment of epilepsy and mood disorders (Orthan 2012; Xu 2012; Kumar 2011; Haleagrahara & Ponnusamy 2010; Visweswari 2010; Dhanasekaran 2009; Barbosa 2008; Gadahad 2008; Wattanathorn 2008; Xu 2008; Mohandas Rao 2007; Mukherjee 2007; Ramanathan 2007; Chen 2005; Rao 2005; Soumyanath 2005; Subathra 2005; Vattanajun 2005; Chen 2003; Gupta 2003; Veerendra Kumar & Gupta 2003, 2002).

Rosmarinic Acid

Rosemary (*Rosmarinus officinalis*) herb contains a number of components with anticancer properties, notably rosmarinic acid, carnosol, carnosic acid and ursolic acid (Ngo 2011).

Rosmarinic acid, which is a caffeic acid derivative, has been identified as a primary active component of *Centella asiatica* extracts showing anticancer (antiproliferative) activity – although other components contribute to this effect, including various triterpenes (ursolic, pomolic, asiatic and corosolic acids, etc.) (Yoshida 2005). Importantly, recent research has suggested that rosmarinic acid has a cognition-enhancing effect that indicates it could be useful for memory disorders (e.g. Alzheimer's disease) – as well as neurodegenerative problems such as amyotrophic lateral sclerosis (Wang 2012; Bulgakov 2011).

Rosmarinic acid has important pharmacological properties and rates among the most notable of the phenolic chemicals. It is prevalent in numerous aromatic Lamiaceae herbs (subfamily Nepetoideae), such as lemon balm, rosemary, sage, thyme, oregano and peppermint. This compound, which is also widespread in the Boraginaceae family, is of interest due to its antioxidant, anti-inflammatory, antiviral and antibacterial attributes. It has the potential to influence diverse inflammatory and spasmodic conditions such as asthma, intestinal disorders and allergies. Rosmarinic acid has been investigated for treating peptic ulcers, atherosclerosis, liver fibrosis, ischaemic heart disease, cataract and retinal disorders, rheumatoid arthritis and infertility (poor sperm motility) (Bulgakov 2011; Petersen & Simmonds 2003). Rosmarinic acid has also shown potent antiviral activity against Japanese encephalitis virus (Swarup 2007).

The cancer chemopreventive effect of rosmarinic acid may well impart a dietary anticancer property to the culinary use of herbs such as Rosemary and Thyme. The compound may also have valuable potential for reducing the side-effects of chemotherapy, and skin-protective effects (against UV light damage). In particular, it has been suggested that rosmarinic acid has a preventive effect against colon carcinogenesis (Karmokar 2012; Sharmila & Manoharan 2012; Bulgakov 2011).

Surprisingly, some studies have found that Mints, notably *Mentha spicata*, generally contain a higher content (mg/g) of rosmarinic acid (19–58 mg) than Rosemary herb (7–10 mg). The level, however, can vary considerably according to the species or variety analysed. Other studies have found moderate amounts (10 mg) in Sage and Spearmint, with low levels in Lavender and Thyme (around 2 and 6.6 mg, respectively). *Melissa officinalis* was another good resource (36–39 mg) – although climatic and soil conditions have a significant influence on yield quality (Shekarchi 2012).

Thirteen species of Mint are found in Australia. *Mentha spicata* is particularly widespread, being naturalised throughout the entire continent and Tasmania. (Upper image courtesy jacilluch, flickr; lower image courtesy Charissa Lansing, flickr)

Melissa officinalis, from Franz Eugen Köhler, *Köhler's Medizinal-Pflanzen*, 1897.

Lemon Balm (*Melissa officinalis*) can be found naturalised from South Australia to Victoria, New South Wales and Tasmania. This herb and the essential oil have good antiviral remedy against the *Herpes simplex* virus with potential for clinical use (Astani 2012; Mazzanti 2008; Schnitzler 2008; Dimitrova 1993; Cohen 1964). Other familiar aromatics (oils and extracts) with similar anti-*Herpes* potential include Peppermint (*Mentha* x *piperita*), Sage (*Salvia officinalis*), Rosemary, Thyme (*Thymus vulgaris*) and Prunella (*Prunella vulgaris*) (Geuenich 2008; Nolkemper 2006; Schuhmacher 2003).

Two rosmarinic acid derivatives are also of pharmacological importance: lithospermic acid B (salvanolic acid B) and rabdosiin. These compounds have anti-inflammatory, antioxidant and kidney-protective properties. In particular, lithospermic acid showed significant experimental effects against diabetic nephropathy (as did rabdosiin), anticancer activity in head and neck squamous cell carcinoma, microcirculatory protection with potential in cerebrovascular and cardiac conditions, and additional cardioprotective (antiatherosclerosis) properties. Rabdosiin also had anti-HIV potential. *Salvia miltiorrhiza* and *Lithospermum erythrorhizon* are good sources of lithospermic acid B, with the latter also yielding rabdosiin (see Bulgakov 2011 for details).

Salvia miltiorrhiza (Chinese Sage) dried root. This herb, known as Dan Shen, is traditionally utilised for treating gynaecological disorders and as a cardiotonic. It is highly respected in Chinese medicine.

Lithospermum erythrorhizon (Red Root Gromwell), Zi Cao, is primarily recommended for treating febrile and inflammatory disorders including skin eruptions, measles and burn injuries.

Gotu Kola is a rather remarkable small weed which even appears to have detoxicant attributes that support its reputation as a blood-purification agent. Investigations of the effects of the herb in arsenic toxicity showed that Gotu Kola had a significant antioxidant effect that reduced cellular damage and provided substantial support for liver function. It also had protective benefits for the kidney and brain – although it was not a chelation agent (Huda-Faujan 2007; Flora & Gupta 2007; Gupta & Flora 2006). This level of protection, which was associated with bioflavonoid components, has potential for reducing the mental effects of lead exposure in children when used in combination with a chelating compound (Ponnusamy 2008; Saxena & Flora 2006). This provides interesting support for its traditional use in China as an antidote to poisoning from wild mushrooms and *Gelsemium elegans* (Chang 1989).

There is, however, a matter of individual sensitivity to the plant. While Gotu Kola appears to be well tolerated in most people, there are some unfortunate individuals who suffer contact dermatitis on exposure to the herb (or asiaticoside). There has also been a report of photosensitisation associated with its use (Gonzalo Garijo 1996; Bilbao 1995; Chopra 1958). While Gotu Kola has rarely been involved in reports of side-effects, it is possible that heavy metal contamination can occur (Tripathi 2012), and that individual sensitivities may involve other forms of allergic reaction. There are also a few reports of hepatotoxic reactions linked to Gotu Kola, but these do not make a lot of sense considering the strong antioxidant, anti-inflammatory and hepatoprotective properties of the herb. It is more likely this could be associated with some form of toxin contamination, herbal substitution or incorrect identification of the plant used for the raw material. For instance, various species of Germander (*Teucrium* spp.) have definitely been linked to hepatotoxicity.

Toxic Jessamine

Gotu Kola has traditionally been utilised as a detoxicant remedy for *Gelsemium* poisoning. There are three species in the *Gelsemium* genus. All are toxic as they contain strychnine-related alkaloids (gelsemine, gelseminine) and cause a form of poisoning that has been compared to Hemlock toxicity (loss of consciousness, paralysis and death). The nectar, which will even poison

The decorative American Yellow Jessamine (*Gelsemium sempervirens*) is one of the toxic ornamental plants that can be found in temperate Australian gardens (New South Wales, Victoria). This vine is the basis of the well-known homoeopathic medicine Gelsemium, which has been utilised for neurological problems. (Image source: Ellis Rowan painting, from Alice Lounsberry, *Southern Wild Flowers and Trees,* Frederick A. Stokes Company, New York, 1901)

bees, has been linked to incidents of poisoning of children who sucked the blossoms.

The depressant effect of the alkaloids once saw the herb used as a nervous system depressant with sedative, analgesic and antispasmodic properties. This also led to its popular use as an asthmatic and whooping cough remedy, albeit the risk of fatalities was high (Dobelis 1986). It was also recommended for the treatment of trigeminal neuralgia and migraine (BHP 1983) – although the homoeopathic preparation would be a much safer alternative. *Gelsemium elegans*, which is known as Heartbreak Grass, is from Southeast Asia and China, and has an equally toxic reputation that even led to its use as a criminal poison. Indeed, in December 2011 the Chinese billionaire Long Liyuan is said to have been poisoned with the drug, which was allegedly put in a cat-meat stew (BBC News Asia, 4 January 2012).

In Chinese medicine, the use of Gotu Kola (*Centella asiatica*) extended far beyond the European recommendations for treating wounds and skin diseases – being utilised for diverse disorders affecting the gastrointestinal, urinary and respiratory tracts. The fresh juice has been taken for uraemia, urinary problems (whitish, muddy urine), throat inflammation, and conditions characterised by agitation, chronic thirst, diarrhoea and vomiting – which is suggestive of conditions such as enteritis due to food poisoning. The decocted herb with lean pork was recommended for whooping cough, or a tea taken for measles. In infectious hepatitis the herb was decocted, sugar added, and the mixture taken twice daily for a week. An infusion prepared from the powdered herb has also been taken for pleurisy, and to ease the aches and pains associated with old wounds (Chang 1989).

Table 4.1 Summary of Recent Investigations of *Centella asiatica*

The table overleaf provides an indication of the remarkable amount of interest that has been expressed in Gotu Kola. This extensive range of investigations attest to the importance of *Centella asiatica* as a medicinal plant – confirming many of its traditional uses, as well as suggesting new avenues of therapeutic value.

Table 4.1 Summary of Recent Investigations of *Centella asiatica*

Medicinal properties	Investigations (author)
Wound-healing studies	Numerous studies have investigated the efficacy of Gotu Kola, asiatic acid and madecassoside as wound-healing agents (Ermertcan 2008; Kimura 2008; Liu 2008; Shetty 2006; Wollina 2006; Hong 2005; Lu 2004a, 2004b; Biswas & Mukherjee 2003; Coldren 2003; MacKay & Miller 2003; Brinkhaus 2000; Widgerow 2000; Maquart 1999; Shukla 1999a, 1999b; Sunilkumar & Shivakumar 1998; Suguna 1996). Promotion of wound healing in cases of diabetic ulcer (Paocharoen 2010). Scar management: strong wound-healing attributes for asiaticoside; can reduce scar formation (Tang 2011); clinical use of Gotu Kola for scar management and stretch marks of pregnancy (Young & Jewell 2000; Widgerow 2000). Cosmetic: extracts have been widely incorporated into creams etc. for an ability to stimulate collagen, aiming to restore skin firmness, elasticity and improve skin appearance. Extracts have also shown a mild UV protective effect (Hashim 2011).
Antimicrobial properties	*Centella asiatica* extract has a very broad spectrum of antimicrobial activity. It has demonstrated antibacterial activity against *Staphylococcus aureus*, as well as antibiotic-resistant strains (MRSA: methicillin-resistant *S. aureus*) (Zaidan 2005). Extracts have activity against diverse gram-positive bacteria (*Bacillus cereus*, *B. megaterium*, *B. subtilis*, *Sarcina lutea*) , gram-negative bacteria (*Aeromonas hydrophila*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella paratyphi*, *S. typhi*, *S. typhimurium*, *Shigella boydii*, *Sh. flexnerii*, *Sh. dysenteriae*, *Vibrio cholerae*, *V. mimicus*, *V. parahaemolyticus*) and anti-fungal activity (*Candida albicans*, *Aspergillus niger*, *Saccharomyces cerevaceae*) (Ullah 2009; Mamtha 2004). Antiviral potential (Zheng 1989): acts as an antiviral attachment agent against pseudorabies virus (Hosni 2006). Anti-herpes virus activity. An additive effect was seen with Mango (*Mangifera indica*) extracts; active components were asiaticoside and mangiferin, respectively (Yoosook 2000). Dental: use of extracts of Gotu Kola and Pomegranate (*Punica granatum*) significantly improved clinical signs of chronic periodontitis (Sastravaha 2005, 2003). Asiaticoside has shown particularly good effects for enhancing periodontal healing (Nowwarote 2012).
Cardiovascular and cerebrovascular	Studies that have indicated the protective properties of Gotu Kola may extend to ischemia and reduction of arterial plaque. This provides support for the use of the herb as a heart tonic and for conditions such as heart attack or stroke. Madecassoside has been identified as a primary active component (Cao 2010; Bian 2008; Li 2007b; Pragada 2004; Cesarone 2001d). Gotu Kola contains cardiac glycosides that may contribute to a cardiotonic effect of the herb (Krishnaiah 2009). Gotu Kola extracts have shown cellular protective effects on the heart with potential for use in preventing the toxic side-effects of some drugs, e.g. the cardiovascular toxicity associated with the antibiotic adriamycin (doxorubicin) that is used in cancer chemotherapy (Gnanapragasam 2007, 2004). Gotu Kola contains a caffeoylquinic acid with anti-thrombotic activity (Satake 2007).
Liver (hepatoprotective)	*Centella asiatica* has shown potential for the treatment of cirrhosis and fibrosis, including bilharzia-induced liver fibrosis due to the schistosomiasis parasite. Chinese investigations of asiaticoside have shown a remarkable hepatoprotective effect on chemical-induced liver injury (Zhang 2010b; Ming 2004; Kartnig 1988). Chronic hepatitis did not respond to its use (Kartnig 1988).
Respiratory tract	Asiaticoside has shown experimental protective effects against septic lung injury (Zhang 2011c, 2008).
Antidiabetic potential	Extracts have shown good potential for blood sugar regulation (Babish 2010; Krishnaiah 2009). The circulatory benefits of Gotu Kola extend to improvement of peripheral circulation in diabetic individuals (Cesaronbe 2001b, 1994). Used to promote wound healing in diabetic individuals (Paocharoen 2010).
Radiation (radioprotective) properties	Gotu Kola has shown significant antioxidant and radioprotective potential. It acts to protect against cellular damage and normalise cellular function in radiation injuries (Joy & Nair 2009; Jayashree 2003; Sharma & Sharma 2005, 2002). Gotu Kola extracts may be valuable for treating radiation treatment side-effects involving taste perception and weight loss (Shobi & Geol 2001). An evaluation of madecassol (asiaticoside) and tetrandrine on skin radiation injuries demonstrated that both products were able to reduce acute radiation reactions due to a significant anti-inflammatory activity. Tetrandrine, a compound isolated from *Stephania tetrandra* and some other *Stephania* species, was particularly effective (Chen 1999). *Note*: Although *S. tetrandra* is not found in Australia, there are four native species of *Stephania*.

Anticancer (anti-tumour and cytotoxicity studies)	The traditional use of Gotu Kola as an anticancer remedy has received experimental support. Extracts have shown cytotoxic and anti-tumour activity in animal studies (Babu 1995). Gotu Kola extracts: experimental anticancer activity in mouse melanoma, human breast cancer and rat glioma cell lines. Flavonoids showed antioxidant and antitumor activity (Pittella 2009). Gotu Kola extracts: apoptosis-inducing effect on breast cancer cells (Babykutty 2008), and in colon cancer studies (Bunpo 2004). Asiatic acid: induced apoptosis in numerous cancer cell lines including colon cancer (Tang 2009), and human melanoma cell lines (skin cancer treatment potential) (Park 2005). Asiaticoside: apoptosis-inducing effect; enhanced the anti-tumour activity of vincristine in cancer cells, which suggests it may be a useful adjunct in cancer chemotherapy (Huang 2004). *Centella asiatica* extract has shown protective activity against genotoxic agents (cyproterone acetate) (Siddique 2008). Immunomodulating and anti-inflammatory properties with chemopreventive or anticancer potential (Punteree 2005, 2004).
Gastrointestinal disorders	Gotu Kola can strengthen the mucosal barrier of the gastrointestinal tract, promoting healing in gastric and duodenal ulcers and protecting against chemical injury, e.g. from aspirin or ethanol (Abdullah 2010; Guo 2004; Cheng 2004; Sairam 2001a; Cheng & Koo 2000). The herb also contains a compound (3,5-dicaffeoyl-4-malonylquinic acid) with potential for use in inflammatory bowel disease (di Paola 2010).
Anti-inflammatory and antiarthritic properties	The herb has long had a reputation as an arthritis cure. A few fresh leaves are eaten daily or it can be air-dried, powdered, and stored for later use. Studies have supported the anti-arthritic activity of Gotu Kola and suggested potential cartilage protective activity that could be useful for osteoarthritic problems. Madecassoside was identified as a significant anti-rheumatic, anti-arthritic, anti-inflammatory and cartilage protective component of extracts (Hartog 2009; Li 2009; Liu 2008a; Li 2007a). Madecassic acid has shown a more potent suppressive effect on some inflammatory mediators than madecassoside (Won 2010). Madecassol (a proprietary preparation) has had some success in the treatment of scleroderma (a chronic systemic autoimmune disease): improving joint pain (arthralgia), mobility of the fingers, and decreased skin indurations (Mowrey 1990, Kartnig 1988). *Centella asiatica* extracts: significant antinociceptive (analgesic) activity comparable to aspirin (but weaker than morphine), and anti-inflammatory activity comparable to mefenamic acid, a NSAID that is also used for menstrual pain (Somchit 2004); asiatic acid demonstrated analgesic and anti-inflammatory activity (Huang 2011).
Neuroprotective (nerve protective) and mood disorders	Gotu Kola: protective effects on brain function including neurodegenerative diseases, protection for ageing process and enhancement of learning and memory (Haleagrahara & Ponnusamy 2010; Dhanasekaran 2009; Kumar 2009; Barbosa 2008; Wattanathorn 2008; Xu 2008; Mukherjee 2007; Rao 2005; Subathra 2005; Gupta 2003; Veerendra Kumar & Gupta 2003, 2002). Nerve regeneration prospects (Mohandas Rao 2007, 2006; Gadahad 2008; Soumyanath 2005). Epilepsy (Visweswari 2010; Vattanajun 2005). Anti-anxiety and anti-depressive activity (Wanasuntronwong 2012; Jana 2010; Chen 2005; Chen 2003). Asiatic acid has shown anti-ischaemic neuroprotective properties in the brain, with potential for use in rehabilitation of stroke patients (Tabassum 2012; Krishnamurthy 2009). Gotu Kola and asiaticoside-derivatives deserve serious consideration for use as neurotoxin-protective agents (Shinomol 2010; Shinomol & Muralidhara 2008a, 2008b; Ramanathan 2007; Jew 2000; Lee 2000; Mook-Jung 1999). Asiaticoside: neurotoxin protection in studies of Parkinson's disease (Xu 2012).
Detoxicant (chemotoxin and heavy metal protection)	Gotu Kola can provide cellular protection against lead and arsenic toxicity (Sainath 2011; Ponnusamy 2008; Saxena & Flora 2006; Flora & Gupta 2007; Gupta & Flora 2006). It is, however, not a chelation agent. This hyperaccumulation effect, though, is not without risk if the plants are wild harvested from sites high in arsenic or lead (Tripathi 2012).
Antiparasitic and insecticidal potential	Antiprotozoal activity against *Entamoeba histolytica* (Jamil 2007). Antifilarial effect: when combined with *Acacia auriculiformis* against *Dirofilaria immitis* in dogs (Jamil 2007). Intestinal helminth infections: moderate anticestodal activity against *Raillietina echinobothrida* (Temjenmongla & Yadav 2005). Leaf extracts showed activity against sheep fluke (*Paramphistomum cervi*) and larvae of malaria mosquito vector (*Anopheles subpictus*) (Bagavan 2009). Larvicidal and mosquitocidal activities against larvae and adults of *Anopheles stephensi.* Combination of Blue Gum (*Eucalyptus globulus*) and Gotu Kola had a synergistic effect (Senthilkumar 2009). Gotu Kola essential oil, however, showed only a mild degree of mosquito-repellent activity. The main constituents of the oil were farnesene, caryophyllene and p-cymol (Rajkumar & Jebanesan 2007).