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Pharmacotherapeutic Potential of Natural Products in Neurological Disorders

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Amritpal Singh Saroya is currently working in the Department of Dravyaguna (Medicinal Plants) at Dhanwantry Ayurvedic College, Chandigarh, India. He graduated (BAMS) from Guru Nanak Dev University, Amritsar, Punjab, India, and completed his postgraduate Ayurveda Vachaspathi degree, MD (Ay) at B.R. Ambedkar Bihar University, Muzaffarpur. After a certificate course in phytochemical techniques at Madras University, he pursued his MSc in Medicinal Plants at Nagaland Open University. He started his career as an Ayurvedic Medical Officer in Sohana and later worked as an herbal consultant for several years. He continued his career as an external faculty member of the National Institute of Pharmaceutical Research, Mohali, and senior lecturer at Lovely Professional University. He is a consultant to TIME IS (Technology Innovation Management Entrepreneur Information Service), a joint Department of Science and Technology, Government of India, and FICCI project. He has worked as an herbal consultant to several national and international organizations. He is well respected in the field of herbal medicinal plants, and he has authored and edited 25 books and published more than 100 research articles in various national and international peer-reviewed journals. He has presented several papers at Indian and international seminars and conferences.

Jaswinder Singh did his MBBS degree from Government Medical College, Amritsar, in 1995. Subsequently, he did MD (Pharmacology) from Government Medical College, Patiala, in 2001. He has worked in various institutions like Nepalgunj Medical College, Nepalgunj, and Government Medical College, Chandigarh, at various posts. Presently, he is working as Professor at Sri Guru Ram Das Institute of Medical Research, Amritsar, in the Department of Pharmacology. Further, he is part of pharmacovigilance committee of the institute. He has a total teaching experience of more than 15 years and teaches MD (Pharmacology), MBBS, BDS, and BSc (Nursing students) courses. Till now, he has published more than 27 research articles in various national and international journals. He is also serving as an editorial board member of two journals. Further, he has acted as an examiner (internal as well as external) for MBBS and BDS students (external) and as coguide for postgraduate students.

Introduction to Herbal Medicine

1

1.1 Some Basic Definitions

Complementary/Alternative Medicine (CAM)
Complementary/alternative medicine is defined as systems of medicine having a diverse range of practices concerned with healthcare. These health practices are neither part of a tradition of a particular country nor combined with the major healthcare system.

Traditional Medicine (TM)
Traditional medicine is also known as ethnomedicine or indigenous medicine. Traditional medicine is a medical system largely build on cultural beliefs as well as practices passed down from one generation to another generation.

Medicinal Plant
A medicinal plant is also addressed as a medicinal herb. A medicinal plant includes plant material in crude (rough) form and may include roots or rhizome, stem, leaves, root bark, stem bark, wood, flowers and fruits and seeds. These plant parts may be whole, disunified or in powder (pulver) form.

Herbal Medicine
Herbal medicine is also known as botanical or phytomedicine. Herbal medicine is comprised of herbs, herbal materials, herbal preparations and finished herbal products. Herbal medicines supply active constituents (when used as standardized herbal extract), parts of plants (roots or rhizome, stem, leaves, root bark, stem bark, wood, flowers and fruits and seeds) or a combination of both.

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Herbal Materials
Herbal materials largely utilize medicinal herbs or plants. Sometimes, resins, gums, gum-resin, oleo-resins, aromatic or essential oils, fixed oils and dried powders are used in the manufacturing of herbal medicines. All these are known as herbal materials.

Herbal Preparations
Herbal preparations are the basis for finished herbal formulations or products. Herbal preparations include powders (pulver), cold infusion, hot infusion, decoction, extract or tincture. Several pharmaceutical procedures are used in production of herbal preparations.

Finished Herbal Products
Finished herbal products constitute herbal preparations, monoherbal (prepared from single herb) or polyherbal (more than one herb). Polyherbal formulation is also known as mixture herbal product. Polyherbal formulations and finished herbal products contain active ingredients and excipients.

Active Constituents
Active constituent is used for herbal medicines or drugs with a therapeutic activity. In several herbal drugs, the active constituents have been identified, and extracts of these herbal drugs have been standardized so as to contain a definite amount of ingredients. In certain cases, where it is difficult to find the active constituent, the entire herbal medicine is considered as one active constituent.

Marker Compound
Marker compound is an ingredient of a herbal drug or plant used for the quality control and assurance purposes in the finished product. A marker compound may (here it is active principle also) or may not have therapeutic utility.

A constituent of a medicinal herb is used for quality control and assurance of herbal product. A marker compound may or may not have therapeutic activity.

1.2 History of Herbal Medicine

As far as history of herbal medicine is concerned, it is not easy to explore the facts. Historical findings are suggestive of the fact that the ancient civilisations used the remedies based on the medicinal plants in the treatment of the diseases.

Primitive man made a strong observation and appreciation of the herbal diversity at his disposal. Initial proof for the use of medicinal herbs as healthcare system is recorded from China way back in 2800 B.C. Much of the therapeutic use of medicinal herbs has been developed through observations of wild animals and by trial and error.

Shen Hung, who lived in 3000 B.C., was a great Chinese emperor. He documented the use of 365 medicinal plants in his work, *Pen-ts'ao Ching*. It is also

popularly known as Divine Husbandman's Materia Medica. The work authored by Shen Hung is seen as primitive Chinese Pharmacopoeia. The salient feature of the work is the documentation of Ma Huang (Ephedra) in the management of respiratory ailments including bronchitis (inflammation of the bronchus) and asthma (difficulty in breathing).

The emperor of Babylonia, Hammurabi, in 1800 B.C. wrote a text on the therapeutic use of medicinal plants. Hammurabi documented the use of peppermint in the treatment of ailments related to the digestive system.

Hippocrates (400 B.C.) created the first herbal text in Greek. He emphasized the role of food, exercise and medicine in the management of optimal health. Galen (200 AD) was a famous practitioner of phytomedicine. He was first to classify the diseases according to the anatomy of the human body. He also documented specific remedies for curing diseases.

Avicenna (1100 AD) was a great Arabic physician. He wrote a text popularly known as the *Canon of Medicine*. Dioscorides was a Roman physician and authored *De Materia Medica*, which included the medicinal use of herbs like almond (*Prunus amygdalus*) and wormwood (*Artemisia absinthium*). *De Materia Medica* is credited as pioneer systematic pharmacopoeia. Translation and preservation were carried out by the Arabs. Finally translation was done into Latin in the tenth century.

Culpepper (1600 AD) included the principles and practices of herbal medicine in the work *The English Physician*. Culpepper included data on 1653 drugs with information on mode of preparation (pharmaceutics) and dose (posology). Many of Culpepper's manuscripts were published after his death. In 1666, many of his manuscripts were lost in the Great Fire of London.

Macus Aurelius (161–180 AD) is credited with explaining the use of opium poppy (*Papaver somniferum* L.) in the treatment of cephalgia, epilepsy, asthma and skin ailments in his popular work known as *Meditations*.

As far as the origin of *Ayurveda*, the traditional Indian system of medicine, is concerned, it is considered to be a branch of *Atharva Veda*. *Ayurveda* developed as a medical system in the Vedic period. It is estimated that around 1000 B.C., two principle texts of Ayurveda, *Charaka Samhita* (text dealing with medicine) and *Sushruta Samhita* (text dealing with surgery), were composed.

The period between 1488 and 1682 is called the age of herbals. Otto Brunfels wrote herbal text in 1488, which was published in 1534. The age of herbals has produced distinguished scientists: Gesner Conard, Hieronymus Bosch, John Parkinson, Leonhard Fuchs and William Turner.

Friedrich Wilhelm Serturner is considered as the pioneer in isolating active constituents from medicinal plants. He first isolated an alkaloid (morphine) from opium poppy (*Papaver somniferum* L.) in the year 1805. Felix Hoffman isolated aspirin (acetylsalicylic acid) from willow bark (*Salix* spp.). Aspirin is a non-steroidal anti-inflammatory drug (NSAID) having important place in the treatment of diseases in cardiology and rheumatology.

The separation of cardiac glycoside, digoxin, was carried out by William Withering from foxglove (*Digitalis purpurea* L.). The discovery of digoxin is

considered to be a milestone in cardiology as digoxin is still a priced drug in the treatment of congestive cardiac failure.

Klie isolated an alkaloid, reserpine, from Sarpagandha (*Rauwolfia serpentina)*, once upon a time a priced drug for the treatment of hypertension (high blood pressure) and insanity (madness). Robiquet discovered the antitussive alkaloid, codeine, from the opium poppy (*Papaver somniferum* L.).

Clark Noble is credited with the discovery of vinca alkaloids (vinblastine and vincristine) from Madagascar periwinkle (*Catharanthus roseus* Linn). Vinca alkaloids have a significant place in oncology.

Isolation of taxol (anticancer agent) from Pacific yew (*Taxus brevifolia* Nutt.) by Mansukh C. Wani and silymarin (hepatoprotective agent) from milk thistle (*Silybum marianum* L.) by Jack Masquelier is a recent example of drug discovery from medicinal plants.

1.3 Renaissance of Herbal Medicine

Sales of the herbal (phyto) drugs in the United States was US$4.5 billion in 1980 and rose to US$15.5 billion in 1990. The sales of herbal drugs in 2013 was estimated to be US$6 billion in the United States alone. Similar trend was witnessed in Europe. As per one estimate, only 5 to 15% of the approximately 250,000 species of higher plants (angiosperms) have been subjected to preliminary phytochemical screening for the detection of bioactives.

The European market for herbal supplements is estimated at over US$2.7 billion and for herbal drugs, a further US$0.9 billion. Germany has been identified as the largest market in terms of exports. The market for herbal drugs is growing rapidly at over 4% per annum. It is comparatively faster as compared to herbal supplements. The herbal drug market has reached saturation, and it is expected to reach its peak at US$6–8 billion in the forthcoming times.

Traditional Chinese medicine (TCM) has achieved and tasted significant success in herbal medicine. Well-developed infrastructure and research facilities are the contributing factors for this success. Medicinal herbs used in traditional Chinese medicine have been extensively subjected to phytochemical and pharmacological screening.

In India, the department of AYUSH (Ayurveda, Yoga, Unani, Siddha and Homoeopathy) has taken several remedial steps to improve standards of Ayurvedic formulations. Good manufacturing practice (GMP) guidelines have formulated to ensure quality control and assurance. Medicinal plant boards have been constituted at state and centre level to attract industry and the farmers for adopting cultivation of medicinal plants. Several multinationals like Ranbaxy and Sun Pharma have diversified into Ayurvedic facility, keeping in mind the renaissance of Ayurvedic medicine.

1.4 Herbal Glossary

Active constituent- a herbal drug or herbal drug preparation and its entirety are regarded as active constituent.
Adaptogen- an agent that invigorates or strengthens the system.
Alterative- an agent used for purifying blood.
Anabolic- an agent having steroidal action.
Analeptic- an agent used to boost respiration and circulation.
Anodyne- an agent that relieves pain on local application.
Antiarrhythmic- an agent used for treatment of heart disease.
Antibiotic- an agent used for killing microorganisms.
Anticoagulant- an agent used for preventing blood clotting.
Antidepressant- an agent used for counteracting depression.
Antihelminthic- an agent used to kill worms.
Antiperiodic- an agent used for preventing relapsing fever.
Antipruritic- an agent used to cure itching.
Antirheumatic- an agent used for curing arthritis and rheumatism.
Analgesic- an agent used for preventing pain.
Anti-inflammatory- an agent used for preventing inflammation.
Antipyretic- an agent used for lowering the fever.
Antiseptic- an agent used form preventing the growth of microorganisms.
Antispasmodic- an agent used for reliving the spasms of voluntary and involuntary muscles.
Aphrodisiac- an agent used to stimulate sex urge and maintain vitality.
Aperient- an agent used for mild laxation.
Ayurveda- the ancient healing system in India.
Bruising- a process of smashing of different parts of a medicinal herb in a pestle and mortar.
Cathartic- an agent used to relieve severe constipation.
Carminative- an agent used to dispel gas from the intestine and prevent distension.
Cholagogue- an agent used to promote the flow of bile.
Choleretic- an agent that stimulates the formation of bile.
Convulsant- an agent which induces seizures.
Counterirritant - (see rubefacient.)
Crude drug- a form of medicinal herb unchanged by processing other than separation of parts, drying or grinding.
Decoction- a process of boiling a coarsely bruised drug in water in tinned pots with covers for a definite period.
Diaphoretic- an agent used for increasing perspiration through the skin.
Diuretic- an agent used for increasing urine flow.
Ecbolic- an agent used for stimulating uterine musculature.
Elutriation- a process of separation of the coarser particles of a powder from the finer ones.

Emetic- an agent used for inducing vomiting.
Emollient- an agent which softens the skin.
Expectorant- an agent used to promote the expulsion of mucus from the respiratory tract.
Expression- a process of pressing out juice or oil from plant products.
Extract- a process of manufacturing concentrated preparations of the active principles of the vegetable drugs.
Fluid extract- a liquid extract of raw plant material, usually of a concentration ratio of 1 part raw herb to 1 part solvent.
Febrifuge- an agent used to reduce fever.
Haemostatic- an agent used to prevent flow of blood.
Hepatoprotective- an agent used for preventing injury to the liver.
Hygroscopic- a substance that readily attracts and retains water.
Hypnotic- an agent used to induce sleep.
Hypolipidemic- an agent which reduces high levels of cholesterol.
Incineration- a process of heating the organic substances with access of air, so that all the carbonaceous matter is burnt.
Infusion- a process of treating a moderately comminuted drug in a muslin bag soaked in cold or hot water.
Levigation- a process of grounding of solid substance with water to make a paste and dry.
Maceration- a process of soaking a ground-up drug in a solvent and expression of fluid from it.
Medicated oil- an oil preparation obtained by steeping the medicinal herb in oil for several days or months.
Sifting- a process of passing a powdered drug through a sieve to obtain a powder of uniform strength.
Nervine- an agent used for improving the function of the nerves.
Nootropic- an agent having memory-enhancing activity.
Rubefacient- an agent used for increasing the blood supply to the skin, when applied locally.
Sedative- an agent used for calming the functional activity of the body.
Standardization- a process of fixing the quantity of active constituent of a medicinal agent.
Stimulant- an agent used for boosting metabolism and circulation.
Stomachic- an agent used to promote stomach function.
Tincture- an alcoholic solution of active constituents of vegetable drugs.
Trituration- a process of rubbing solid substances into finer ones with the help of a pestle and mortar.
Tonic- an agent used to increase energy and vigour in a specific part of the body.
Vasodilator- an agent used to dilate the blood vessels.
Vulnerary- an agent used to promote the healing of new cuts and wounds.

Medicinal Herbs Used in Herbal Medicine for Neurological Disorders

2

2.1 *Albizia julibrissin* Baker (Fabaceae)

A. julibrissin is native to Asia and popularly known as Persian silk tree. In traditional Chinese medicine, it is used to treat anxiety and depression. The plant is reported to contain flavonoids (Wei and Guo 2015).

2.2 *Acorus gramineus* Sol. Aiton (Acoraceae)

This plant is commonly known as Japanese sweet flag. The plant has sedative properties and is widely used in traditional Chinese medicine. In Korea the plant is used to treat neurasthenia. Phytochemically, the essential oil contains α-, β- and γ-asarone (Fig. 2.1).

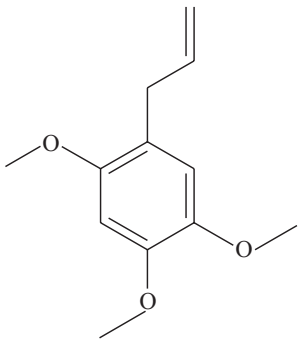

Fig. 2.1 Structure of γ-asarone

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2.3 *Acorus tatarinowii* Schott (Acoraceae)

Green leaf calamus plant is the common name of *A. tatarinowii.* In traditional Chinese medicine, the plant finds use in the treatment of Alzheimer's disease. It is a rich source of lignans. The decoction and volatile oil extracted from the rhizome has antiepileptic effects (Liao et al. 2005). Research has shown that *A. tatarinowii* extract protects PC12 cells from amyloid-beta-induced neurotoxicity (An et al. 2014).

2.4 *Amphilophium crucigerum* (L.) L.G.Lohmann (Bignoniaceae)

Monkey's comb is the common name of this plant. The seeds find wide use in the treatment of neuropathic pain *(*De Prá et al. 2017).

2.5 *Galphimia glauca* Cav. (Malpighiaceae)

G. glauca is found in tropical Africa. Triterpenes and triterpenes galphimine A, B and C are found in the plant. In Mexican traditional medicine, a tea prepared from the plant is used to soothen the nerves and to treat anxiety (Guzmán-Gutiérrez et al. 2014). Nor-seco-triterpenes (galphimines) are the main chemical constituents (Herrera-Ruiz et al. 2006). Two clinical studies utilizing a standardized herbal preparation and extract (standardized in 0.175 mg of galphimine B) (Fig. 2.2) showed that the latter has greater anxiolytic effectiveness as compared to lorazepam (Herrera-Arellano et al. 2007, 2012).

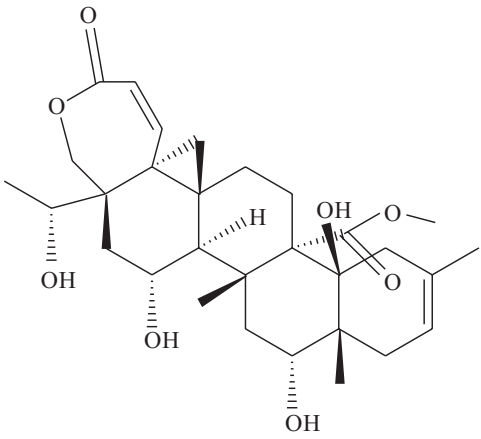

Fig. 2.2 Structure of galphimine B

2.6 *Hypoxis hemerocallidea* Fisch. & C. A. Mey. (Hypoxidaceae)

In South African ethnomedicine, the extracts of African potato are used for the treatment of childhood convulsions and epilepsy. The aqueous extract of the corm is reported to have anticonvulsant activity against bicuculline, pentylenetetrazole, picrotoxin-induced seizures in mice (Ojewole 2008).

2.7 *Litsea glaucescens* Kunth (Lauraceae)

The common name of *L. glaucescens* is Mexican bay leaf and is found in Central America. β-Pinene and linalool are major constituents of the essential oil. In Mexican traditional medicine, the plant is used in the treatment of sadness (Gutiérrez, Chilpa & Jaime, 2014). The ancient claim has been validated by antidepressant-like activity of the essential oil (Guzmán-Gutiérrez et al. 2012).

2.8 *Leonurus sibiricus* L. (Lamiaceae)

Siberian motherwort is native to China, Manchuria, Mongolia and Siberia. A tincture prepared from the dried-flowering tops and leaves is used to calm the nerves. A tea is also used for the same purpose as the tincture. Leonurine (Fig. 2.3) is the active alkaloid.

2.9 *Melissa officinalis* L. (Lamiaceae)

This plant is known by several names including lemon balm, balm, common balm and balm mint. In Australian ethnomedicine, the essential oil in *M. officinalis* is used in the treatment of neurological diseases. A tea prepared from the plant is also used for inducing sleep. For details please refer to the chapter.

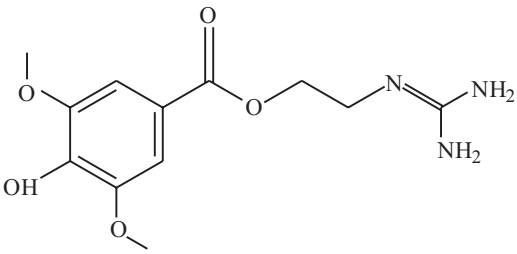

Fig. 2.3 Structure of leonurine

2.10 *Nepeta cataria* L. (Lamiaceae)

N. cataria is popularly known as catmint or catnip. The essential oil contains a monoterpene, nepetalactone (Fig. 2.4). It is widely used in the treatment of restlessness and nervousness.

2.11 *Nepeta hindostana* (Roth) Haines (Lamiaceae)

N. hindostana is an important plant of Unani system of medicine. In this system, the plant is popularly known as Badranjboya (Ahmad et al. 1986a). The English name is Nepeta Herb. It contains triterpenoid, nepeticin (Ahmad et al. 1986b; Ahmad and Bano 1981); triterpene acid, 2α,3β,23-trihydroxyurs-12-en-28-oic acid (Fig. 2.5); and triterpenoidal aldehyde, nepehinal (Ahmad and Bano 1981). It has central nervous system depressant and sedative activities and is given to treat anxiety. The fruit is given in hypochondriasis.

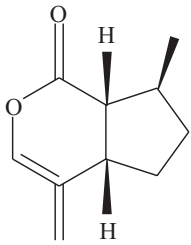

Fig. 2.4 Structure of nepetalactone

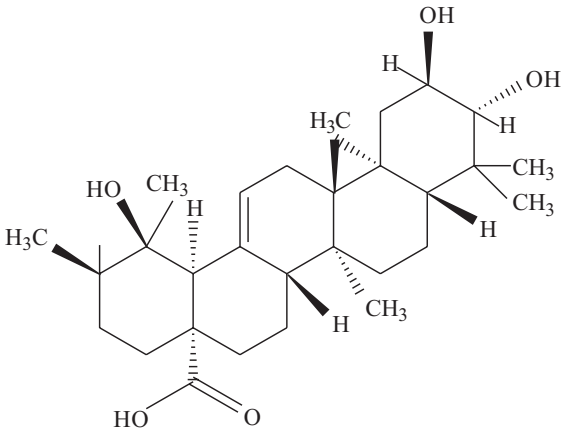

Fig. 2.5 Structure of 2α,3β,23-trihydroxyurs-12-en-28-oic acid (asiatic acid)

2.12 *Petiveria alliacea* L.

P. alliacea grows in the tropical and specific regions of Africa. The plant has anaesthetic and sedative properties. It is used in traditional medicine for the treatment of anxiety, pain, memory deficits and seizures (Luz et al. 2016).

2.13 *Salvia guaranitica* St. Hil. (Lamiaceae)

S. guaranitica St. Hil. is a traditional medicinal plant used in Latin America as sedative. Cirsiliol, a flavonoid in *S. guaranitica* extracts, is a competitive low-affinity benzodiazepine receptor ligand (Marder et al. 1996). A partially purified fraction and the active principle, cirsiliol (a flavonoid) (Fig. 2.6), exhibited sedative and hypnotic effects (Viola et al. 1997).

2.14 *Sceletium tortuosum* (L.) N.E. Brown (Aizoaceae)

S. tortuosum is commonly distributed in South Africa. It is popularly known as Kanna. The plant is used as mood elevator, anxiolytic and antistress in traditional medicine (Gericke and Viljoen 2008). Mesembrine (Fig. 2.7) is the major alkaloid (Harvey et al. 2011). An in vivo study does not demonstrate a potential effect of *S. tortuosum* on restraint-induced anxiety (Smith 2011). *S. tortuosum* containing high content of mesembrine having serotonin reuptake inhibition activity is secondary to monoamine oxidase-inhibiting activity (Coetzee et al. 2016). Mesembrenone (Fig. 2.8), another alkaloid, has prominent serotonin reuptake inhibition activity (Harvey et al. 2011).

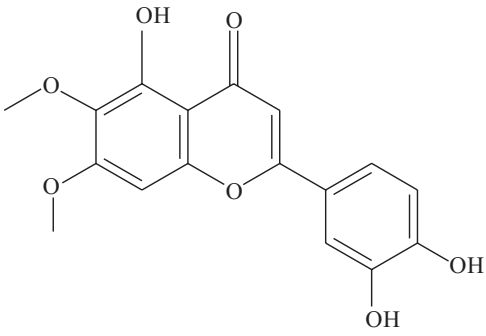

Fig. 2.6 Structure of cirsiliol

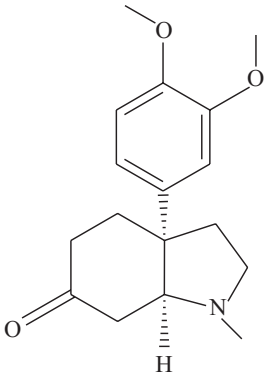

Fig. 2.7 Structure of mesembrine

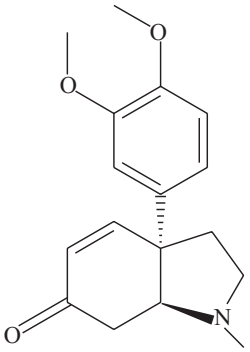

Fig. 2.8 Structure of mesembrenone

2.15 *Sorbus alnifolia* (Sieb. et Zucc.) K. Koch (Rosaceae)

Korean mountain ash is the common name. The plant finds application in the treatment of neurological disorders in ethnomedicine in Korea. The methanolic extract has protective effect on dopaminergic neurodegeneration in *Caenorhabditis elegans* (Cheon et al. 2017).

2.16 *Stereospermum kunthianum* Cham. (Bignoniaceae)

This plant is commonly known as pink jacaranda and is native to Africa. Coumarins and sterols are the main phytochemicals present in the plant. In Nigeria, the plant is used in the treatment of febrile convulsions in infants and young children. The extract of the stem bark has protective activity against generalized seizures in electroconvulsive and pentylenetetrazole models in rodents (Ching et al. 2009).

2.17 *Tilia tomentosa* Moench (Tiliaceae)

Silver lime is native to southeastern Europe and southwestern Asia. *T. tomentosa* is widely used in Latin America traditional medicine as sedative and tranquilizer. A complex fraction containing unidentified constituents demonstrated anxiolytic activity in animal tests (Viola et al. 1994).

2.18 *Verbena officinalis* L. (Verbenaceae)

Common verbena is native to Europe. In traditional medicine, it is used as antidepressant. Iridoid glycosides, hastatoside (Fig. 2.9) and verbenalin (Fig. 2.10) have been identified as sleep-inducing agents in the plant (Makino et al. 2009).

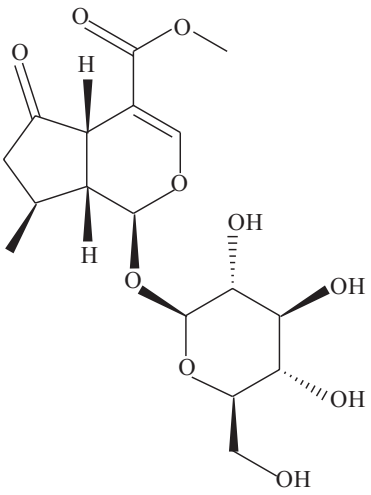

Fig. 2.9 Structure of hastatoside

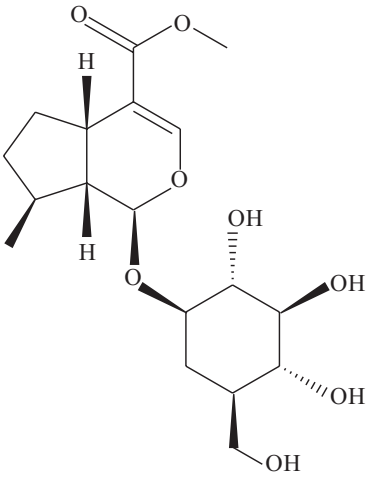

Fig. 2.10 Structure of verbenalin

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Neuropharmacology of Genus *Hypericum*: Hypericin and Hyperforin

3

3.1 *Hypericum perforatum* Linn. (Guttiferae)

H. perforatum is known by various names including Amber touch-and-heal, balm-of-warrior's wound, devil's scourge, god's wonder plant, Klamath weed, goatweed, perforate St John's wort, rosin rose, touch and heal and witcher's herb. However, St John's wort is widely and popularly used common name of *H. perforatum* (Upton 1997). The word St John's wort is given to plant because it was harvested on the occasion of St John's day, which falls on 24th of the June (Gunther 1968).

3.2 Habitat

H. perforatum is native to North Africa, West Asia and Europe. In the United States, the herb grows abundantly in Northern California. The drug is imported from Eastern Europe (Upton 1997).

3.3 Botany

H. perforatum is a perennial, erect and glabrous herb. Roots are fusiform and branched. Stem is round having distinct lengthwise ridges. Leaves are oblong, opposite, sessile, blue-green, translucently dotted and having pale lower surface. Flowers are pentamerous and yellow in colour. Fruit is ovate and triangular capsule. Seeds are minute and cylindrical (Bombardelli and Morazzoni 1995).

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_3

3.4 Traditional Use in Treatment of Diseases of the Nervous System

In European system of medicine, *H. perforatum* is used as an antidepressant and anxiolytic agent (Rasmussen 1998; Butterweck 2003). In America, medical herbalists use the plant in the treatment of nervous depression (Leung and Foster 1996).

3.5 Chemistry

3.5.1 Napthodianthrones

Napthodianthrones are derived from anthracene (an aromatic hydrocarbon). Hypericin, pseudohypericin and isohypericin are the major napthodianthrones of *H. perforatum*. The fresh plant of *H. perforatum* contains the precursor compounds, protohypericin and protopseudohypericin. In the presence of sunlight, the protohypericin and protopseudohypericin are converted into hypericin and pseudohypericin, respectively (Bruneton 1995) (Figs. 3.1 and 3.2).

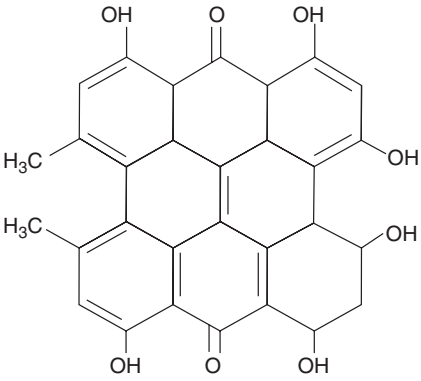


Fig. 3.1 Structure of hypericin

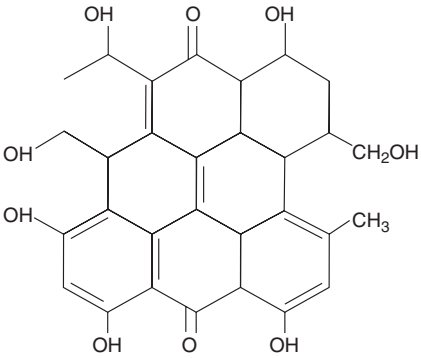


Fig. 3.2 Structure of pseudohypericin

The total amount of napthodianthrones ranges from 0.05 to 0.15% (Newall et al. 1996). The hypericin content of dried flowers can be up to 1.8% (Upton 1997). In majority of the clinical trials, a standardized extract containing 0.3% hypericin has been used.

3.5.2 Acylphloroglucinols

Acylphloroglucinols are reported in fresh crop of *H. perforatum* (Erdelmeier 1998). The chief acylphloroglucinols found in *H. perforatum* are hyperforin and adhyperforin (Maisenbacher and Kovar 1992; Erdelmeier 1998) (Figs. 3.3 and 3.4).

3.5.3 Flavonoids

Hyperoside (hyperin), quercetin, isoquercetin, rutin, methyhespericin, isoquercitrin, quercitrin, I-3/II-8-biapigenin (amentoflavone), kaempferol (Koget 1972; Berghoefer and Hoelzl 1987; Butterweck et al. 2000). In addition, miquelianin and astilbin have been reported (Baureithel et al. 1997) (Figs. 3.5, 3.6, 3.7, 3.8, 3.9, and 3.10).

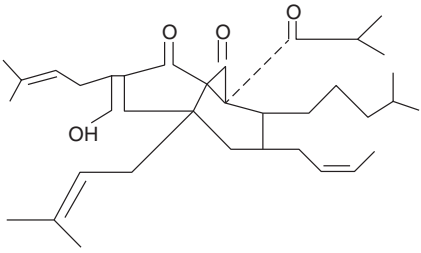


Fig. 3.3 Structure of hyperforin

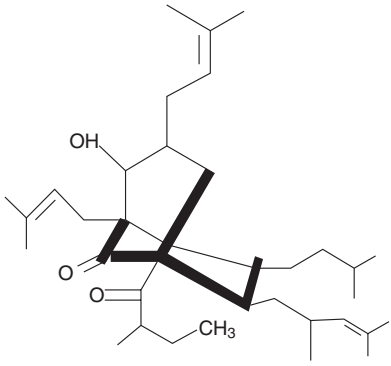


Fig. 3.4 Structure of adhyperforin

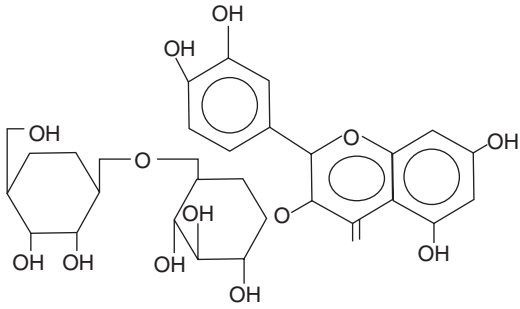


Fig. 3.5 Structure of rutin

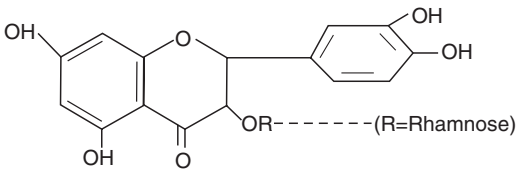


Fig. 3.6 Structure of quercitrin

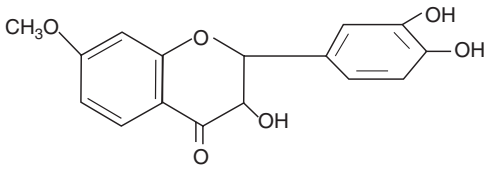


Fig. 3.7 Structure of rhamnetin

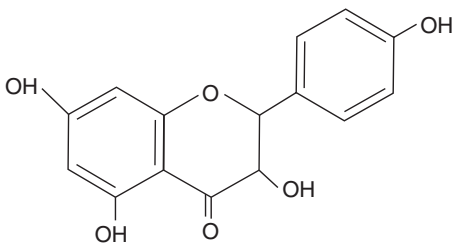


Fig. 3.8 Structure of kaempferol

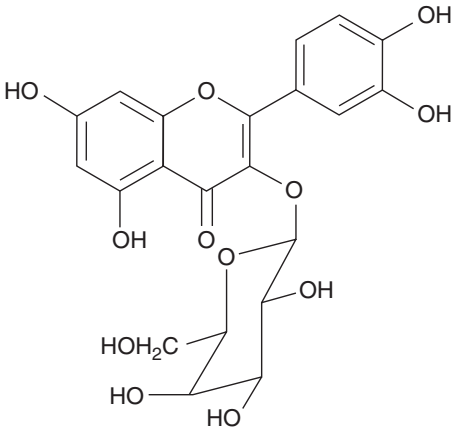


Fig. 3.9 Structure of hyperoside

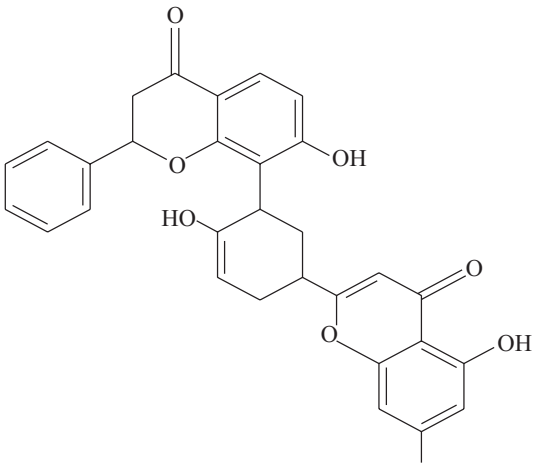


Fig. 3.10 Structure of amentoflavone

3.5.4 Flavanols

Catechin-type tannins and condensed proanthocyandins (catechin, leucocyanidin and (-)-epicatechin (Kitanov 1983) (Fig. 3.11)

3.5.5 Xanthones and Sterols (Mathis and Ourisson 1964)

3.5.6 Terpenoids

Monoterpenes including α-pinene, β-pinene, myrcene, limonene and sesquiterpenes including caryophyllene and humulene (Sticher 1977)

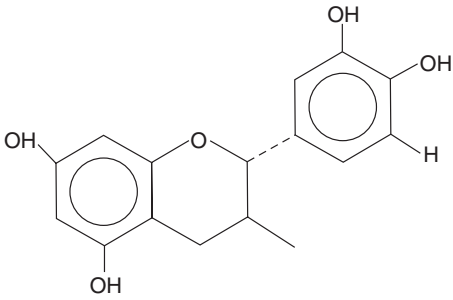


Fig. 3.11 Structure of catechin

3.6 Neuropharmacology of *H. perforatum* Extract

3.6.1 Non-clinical Studies

3.6.1.1 Antidepressant Activity

H. perforatum extract with known amount of the napthodianthrone, hypericin, in a foreign environment, enhanced the exploratory activity of mice. Further, the extract in a dose-dependent fashion resulted in prolonging the narcotic sleeping time and in the water wheel test, significantly enhancing the activity of mice (Okpanyi and Weischer 1987).

Two investigatory studies explored possible role of *H. perforatum* extract as monoamine oxidase inhibitor. In the first study, the extract of *H. perforatum* and all the fractions resulted in a significant inhibition of MAO-A. The flavonoid-rich fraction and other fractions showed an inhibition of 39% and less than 25%. However, the study failed to confirm the monoamine oxidase inhibition was the underlying mechanism behind antidepressant activity (Bladt and Wagner 1994).

The second study showed an inhibition of monoamine oxidase with *H. perforatum* total extract to 10(−4) mol/L, hypericin to 10(−3) mol/L and one extract fraction containing hypericins and flavonols up to 10(−5). Just like the previous one, this study also failed to explain the monoamine oxidase inhibition as the possible mechanism behind antidepressant activity (Thiede and Walper 1994).

In a study, *H. perforatum* extract (6.2 micrograms/ml) caused a 50% inhibition of serotonin (5-hydroxytryptamine). An inhibition of serotonin by postsynaptic receptors was the possible mechanism involved in antidepressant activity of *H. perforatum* extract (Perovic and Muller 1995).

A standardized extract of *H. perforatum* inhibited monoamine oxidase A and monoamine oxidase B inhibiting activity in a weak fashion. The extract inhibited the synaptosomal uptake of neurotransmitters (dopamine, norepinephrine and serotonin) with equal affinity – 2 micrograms/ml. The antidepressant action of *H. perforatum* extract was comparable with standard antidepressants (Muller et al. 1997).

In yet another investigational study, Indian *H. perforatum* and imipramine significantly reduced the immobility time in behavioural despair and tail suspension tests. The antidepressant activity of Indian *H. perforatum* was comparable to the tricyclic antidepressant, imipramine (Kumar et al. 1999).

H. perforatum inhibited uptake of serotonin and norepinephrine in astrocytes which may be responsible for antidepressants activity Neary and Bu 1999). Interleukin-6 has been postulated to be a necessary compound contributing to the antidepressant action of *H. perforatum*, as it mediates the effect by activating the serotonin system (Calapai et al. 2001a).

It seems to be that activation of dopaminergic, noradrenergic and serotonergic system is involved in the antidepressant action of a *H. perforatum* extract standardized to 0.3% hypericin and 4.5% hyperforin and flavonoids (50%) (Calapai et al. 2001b). In the forced swimming test, rutin (a flavonoid) has been shown to be essential for the antidepressant activity of ethanolic and methanolic extracts of *H. perforatum* extracts (Nöldner and Schötz 2002) .

In vivo study has shown that indirect activation of sigma receptors by *H. perforatum* extract may be a novel mode of antidepressant activity (Mennini and Gobbi 2004). On mice using the forced swimming and tail suspension methods, *H. perforatum* demonstrated significant antidepressant activity as evident from higher activity of the animals (Bach-Rojecky et al. 2004). Combining the *H. perforatum* extract and quercetin in certain proportion demonstrated significant synergistic antidepressant effect in ICR (a strain of albino) mice (Liu et al. 2013).

3.6.1.2 Anxiolytic Activity

The Indian *H. perforatum* extract demonstrated significant anxiolytic activity in all the tests. The effects induced by 50% ethanolic extract of Indian *H. perforatum* extract were, however, less marked than as compared to lorazepam (Kumar et al. 2000). The results of an observational study in different anxiety models suggested that *H. perforatum* extract demonstrated anxiolytic-like effects in parameters related to generalized anxiety (Flausino Jr et al. 2002).

After subacute treatment, paroxetine at a dose of 5 mg/kg resulted in impaired inhibitory avoidance. *H. perforatum* administered repeatedly at a dose of 300 mg/kg induced an anxiolytic effect. It was apparent from decrease in inhibitory avoidance and an antipanic effect evident from increase in one-way escape (Beijamini and Andreatini 2003). A study explained the utility of *H. perforatum* in the management of sleep deprivation-induced anxiety-like behaviour (Kumar and Singh 2007).

In an experimental study involving rat model related to type 2 diabetes, *H. perforatum* demonstrated beneficial effect on anxiety and depression (Husain et al. 2011). In an experimental study involving streptozotocin-diabetic rats, *H. perforatum* extract (125 and 250 mg/kg for 7 days) resulted in significant improvement in impaired parameters (Can et al. 2011b) (Fig. 3.12).

3.6.1.3 Anti-dementia Activity

The mice fed with *H. perforatum* extract containing 5% hyperforin showed significant reduction of parenchymal beta-amyloid accumulation and moderate, but statistically significant, increases in cerebrovascular P-glycoprotein expression. The study concluded the fact that *H. perforatum* extract may slow down the progress of Alzheimer's disease (Brenn et al. 2014).

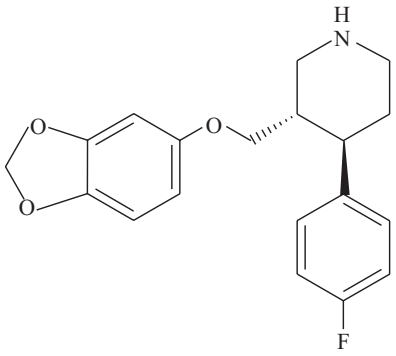


Fig. 3.12 Structure of paroxetine

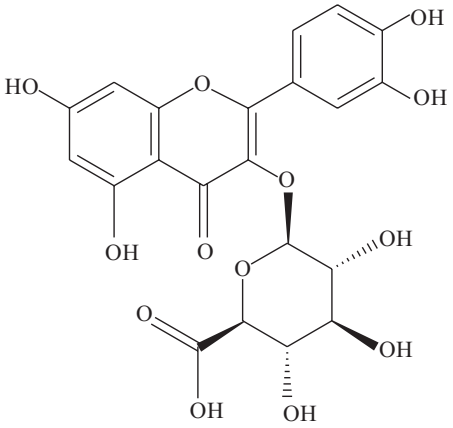


Fig. 3.13 Structure of miquelianin

3.6.1.4 Antistress Activity

Indian *H. perforatum* (100 and 200 mg/kg, p.o.) attenuated foot shock stress-induced perturbations in albino rats. The antistress activity of Indian *H. perforatum* was comparable to *Panax ginseng* (Kumar et al. 2001). *H. perforatum* extract and *two compounds* (amentoflavone and miquelianin) have been reported to decrease stress-induced hyperthermia (elevated body temperature) in mice (Grundmann et al. 2006) (Fig. 3.13).

3.6.1.5 Neuroprotective Activity

The neuroprotective activity of a standardized extract of *H. perforatum* containing acylphloroglucinol (hyperforin) and flavonoid (quercetin) has been reported on rotenone-induced Parkinson's disease in rats (Gómez del Rio et al. 2013) (Fig. 3.14).

The hydroalcoholic extract of *H. perforatum* reduced the motor dysfunction and showed neuroprotective activity in intrastriatal 6-hydroxydopamine (oxidopamine) animal model of paralytic agitans or Parkinson's disease (PD) (Kiasalari et al. 2016) (Fig. 3.15).

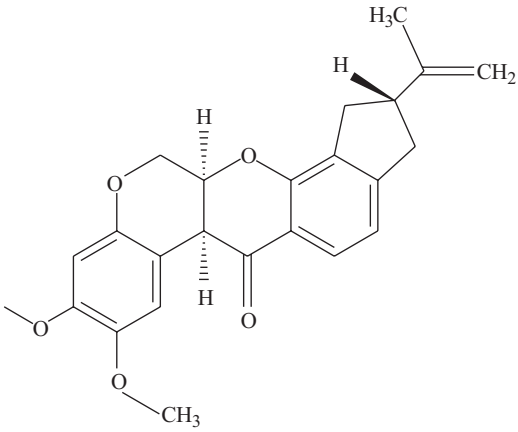


Fig 3.14 Structure of rotenone

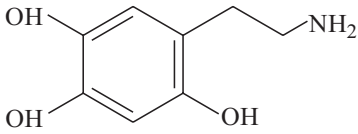


Fig. 3.15 Structure of 6-hydroxydopamine

3.7 Neuropharmacology of Hypericin

3.7.1 Non-clinical

Initial studies reported promising role of hypericin in the treatment of depression (Wenzel 1959; Hoffmann and Kühl 1979). Solubilized napthodianthrones from *H. perforatum* showed significant antidepressant activity in the forced swimming test. Procyanidins, particularly procyanidin B2, significantly increased in vivo effects of the hypericin and pseudohypericin (Butterweck et al. 1998).

A study exploring the possible antidepressant action of hypericin reported an increase in the neuronal action potential duration by extracellularly applied hypericin. This might be ascribed to the effect of hypericin on I(A) and I(K) currents (Wang et al. 2010b).

In another study, hypericin was reported to suppress Ca2+ channel dependent on voltage and mitogen-activated protein kinase activity. While doing this, hypericin caused inhibition of release of glutamate (Chang and Wang 2010).

3.7.2 Clinical

H. perforatum extract resulted in significant increase in 3-methoxy-4-hydroxyphenylglycol (a metabolite of norepinephrine degradation), an expression

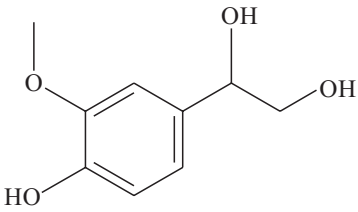


Fig. 3.16 Structure of hydroxyphenylglucol

of a beginning antidepressant reaction as measured in women (age group of 55–65 years and 6 in number) with history of depression (Müldner and Zöller 1984) (Fig. 3.16).

Note: Please see work by Thiede and Walper 1994 regarding inhibition of monoamine oxidase by hypericin.

3.8 Neuropharmacology of Pseudohypericin

The researchers investigated corticotropic-releasing hormone (1) receptors antagonist activity of hyperforin, hypericin and pseudohypericin on corticotropic-releasing hormone-stimulated cyclic adenosine monophosphate (cAMP) synthesis in the ovarian cells of recombinant Chinese hamster. Napthodianthrone, pseudohypericin, showed antagonistic activity on corticotropic-releasing hormone. The study ended with the conclusion that pseudohypericin also contributes to the antidepressant activity of *H. perforatum* (Simmen et al. 2003).

3.9 Neuropharmacology of *H. perforatum* Xanthones

A xanthone-enriched fraction from Indian *H. perforatum* administered to rats and hyperforin-enriched fraction (5 mg/kg p.o.) showed potential activity in the forced swimming test. When both fractions were combined in suboptimal dosages of 2.5 mg each, it demonstrated a significant antidepressant effect in comparison to either hyperforin-enriched or the xanthone-enriched fraction (Muruganandam et al. 2000).

3.10 Neuropharmacology of *H. perforatum* Flavonoids

The flavonoid fraction obtained from *H. perforatum* was separated into two subfractions. Both subfractions with varied doses showed fair response in forced swimming test. Hyperoside was identified as chief constituent in first subfraction. Small quantities of astiblin and hyperoside were detected in the second subfraction (Butterweck et al. 2000).

3.11 Neuropharmacology of Hyperforin

3.11.1 Non-clinical

The researchers identified hyperforin as the unspecific reuptake inhibitor of *H. perforatum* extracts with half-maximal inhibitory concentrations for the three synaptosomal uptake systems mentioned above between 80 and 200 nmol/l (Müller et al. 1998). In the presence of amiloride, methylisobutyl amiloride, benzamil and ethylisopropylamiloride, hyperforin reduced uptake of neurotransmitters (gamma-aminobutyric acid (GABA) and L-glutamate). Hyperforin resulted in elevation of free intracellular sodium which was the mechanism involved in inhibition of serotonin reuptake.

As per results of an in vitro study, the fact underlying the antidepressant property of hyperforin was increased concentrations of neurotransmitters, glutamate and monoamines in the synaptic cleft, probably due to uptake inhibition (Kaehler et al. 1999). A possible role of amiloride-sensitive Na+ channels and Na+-H+ exchangers has been explained behind the antidepressant activity of hyperforin (Wonnemann et al. 2000).

As per new proposed mechanism, hyperforin inhibited the neuronal uptake of dopamine, gamma-aminobutyric acid, norepinephrine and serotonin (Muller et al. 2001). In the same concentration range, hyperforin caused inhibition of several neurotransmitter uptake systems. It also resulted in modulation of ionic conductance mechanisms (Eckert and Muller 2001).

Hyperforin conjugates exhibited significant antidepressant activity as evident from reduction in immobility period in the forced swimming test in rats in comparison to *H. perforatum* extracts containing acylphloroglucinols (hyperforin and adhyperforin) in free state (Muruganandam et al. 2001).

In the forced swimming test, the ester derivative IDN 5491 (hyperforin-trimethoxybenzoate) demonstrated antidepressant-like activity (Bombardelli et al. 2002) (Fig. 3.17).

In the forced swimming test, administration of hyperforin at a dose of 5–20 mg/kg caused significant reduction in the immobility time of rats. To study the possible mode of antidepressant action, a daily treatment of 10 mg/kg for 7 consecutive days was essential in the learned helplessness test. Hyperforin acetate at a dose of 3–5 mg/kg demonstrated an anxiolytic effect (Zanoli et al. 2002) (Fig. 3.18).

Hyperforin dicyclohexylammonium, a stable salt of hyperforin, has been developed (Fig. 3.19).

3.11.2 Clinical

A randomized, double-blind, placebo-controlled, multicentre clinical study demonstrated that the therapeutic utility of *H. perforatum* extract in treating mild to

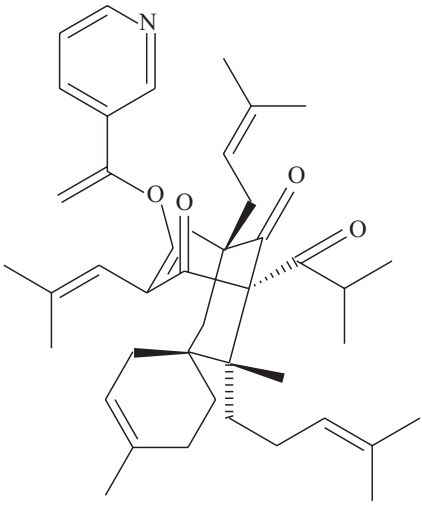


Fig. 3.17 Structure of hyperforin-trimethoxybenzoate

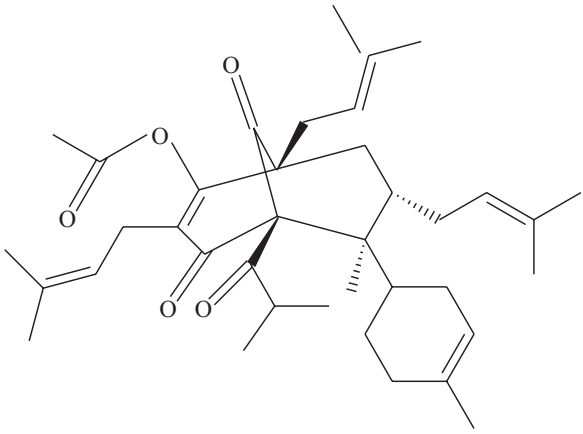


Fig. 3.18 Structure of hyperforin acetate

moderate depression is dependent on the hyperforin content. One hundred forty-seven male and female outpatients diagnosed with mild or moderate depression during the 6 weeks received three treatment groups:

- 3 × 1 tablets of either placebo
- *H. perforatum* extract (300 mg containing of 0.5% hyperforin)
- *H. perforatum* extract (300 mg containing 5% hyperforin)

H. perforatum extract containing 5% hyperforin proved to be superior to placebo in treating symptoms of depression. Nearly same results were witnessed with *H. perforatum* extract containing 0.5% hyperforin and placebo (Laakmann et al. 1998).

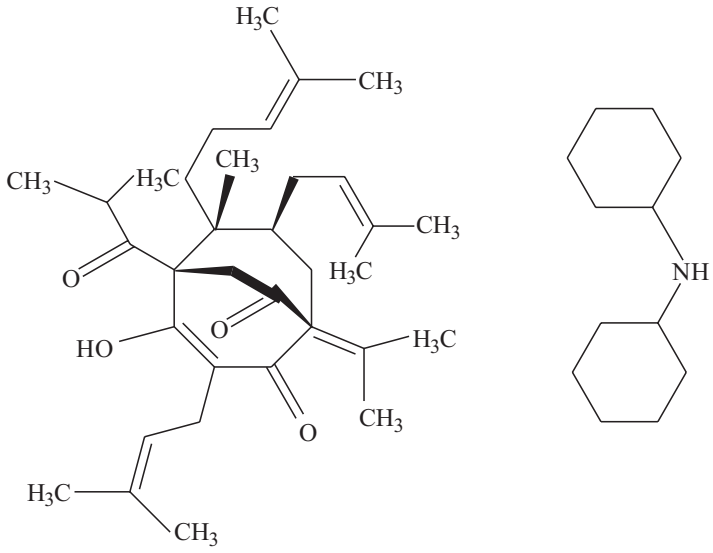
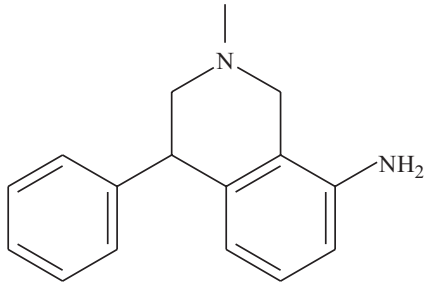


Fig. 3.19 Structure of hyperforin dicyclohexylammonium

Fig. 3.20 Structure of nomifensine



3.12 Neuropharmacology of Adhyperforin

Adhyperforin inhibited binding of [3H]WIN 35,428, a cocaine analogue, to the dopamine transporter. Imipramine (tricyclic antidepressant), nomifensine (norepinephrine-dopamine reuptake inhibitor) and fluoxetine (selective serotonin reuptake inhibitor) inhibited binding of [3H]WIN 35,428, indicating that the binding site of adhyperforin on the dopamine transporter is different from the antidepressant agents (Jensen et al. 2001) (Fig. 3.20).

Adhyperforin showed a significant inhibiting profile in dopamine, GABA, L-glutamate, norepinephrine and serotonin uptake systems (Wonnemann et al. 2001). In forced swimming test and tail suspension assay, adhyperforin caused reduction in the immobility time of mice. Further, adhyperforin inhibited uptake of dopamine,

norepinephrine and serotonin. The compound also demonstrated long-lasting binding affinity for norepinephrine and serotonin transporters (Tian et al. 2014).

3.13 Clinical Pharmacology of *H. perforatum* Extract

3.13.1 Clinical Trials in Depression

3.13.1.1 Mild to Moderate Depression

1. A placebo-controlled, randomized, double-blind trial including patients diagnosed with mild to moderate depression reported that the group receiving the extract of *H. perforatum* showed 66.6% improvement in symptoms of depression as compared to 26.7% with placebo. No adverse reaction was reported (Schmidt and Sommer 1993).
2. In yet another placebo-controlled double-blind study, the efficacy of *H. perforatum* (3 x 300 mg) or placebo was investigated in 105 patients suffering from mild depression. The group that received the extract of *H. perforatum* showed 67% improvement in symptoms of depression as compared to 28% with placebo (Sommer and Harrer 1994).
3. A double-blind study aimed at investigating the efficacy of the extract of *H. perforatum* or with placebo in 72 patients suffering from depression. A significant improvement was noticed in the original placebo group after shifting the placebo group to active treatment during the 5th to 6th week of the therapy (Hansgen et al. 1994).
4. In a randomized, placebo-controlled, double-blind study, the effect of extract of *H. perforatum* was investigated in 39 patients with depression with somatic symptoms. Seventy percent of the patients treated with extract of *H. perforatum* were free of symptoms after 28 days (Hubner et al. 1994).
5. A multicentre, placebo-controlled, double-blind trial studied the effect of 100–120 mg of the *H. perforatum* in 97 patients diagnosed with depression. Significant improvement in the symptoms of depression was noticed. *H. perforatum* also demonstrated an antianxiety effect (Witte et al. 1995).

3.13.1.2 Severe Major Depression

A double-blind, randomized, placebo-controlled trial explored the efficacy of *H. perforatum* extract in treating severe major depression. The patients were assigned 900 to 1500 mg of *H. perforatum* daily. Sertraline was recommended in a dose from 50 to 100 mg daily. Sertraline showed better response than placebo on the Clinical Global Impressions-Improvement scale. Side effect profile of *H. perforatum* and sertraline was different relatively to placebo (Davidson et al. 2002).

3.13.2 *Hypericum* and Seasonal Affective Disorder (SAD)

A study lasting for 28 days reported a striking reduction in the total score of the Hamilton Depression Rating Scale using 900 mg of *H. perforatum* in patients diagnosed with seasonal affective disorder (Kasper 1997).

3.13.3 *Hypericum* and Obsessive-Compulsive Disorder (OCD)

Twelve subjects were evaluated with a primary DSM-IV diagnosis of obsessive-compulsive disorder of at least 1-year duration. Treatment was given for a period of 3 months (450 mg of 0.3% hypericin) twice daily. Significant improvement was observed with a drop in Yale-Brown Obsessive-Compulsive Scale score as observed in clinical trials (Taylor and Kobak 2000) (Fig. 3.21).

3.13.4 Comparative Trials with Synthetic Drugs

3.13.4.1 *Hypericum* Extract vs Maprotiline

The observations of a randomized double-blind study, comparing the effect of *H. perforatum* extract with maprotiline (the tetracyclic antidepressant) in 24 healthy volunteers, showed improved cognitive functions with *H. perforatum* extract (Johnson et al. 1994).

A multicentre double-blind study investigated the efficacy and tolerance of *H. perforatum* extract in comparison to maprotiline in 102 patients diagnosed with depression. The onset of the antidepressant effect was observed earlier with maprotiline. Also, maprotiline treatment resulted in noticeable side effects like drymouth, tiredness and heart complaints (Harrer et al. 1994) (Fig. 3.22).

3.13.4.2 *Hypericum* Extract Versus Imipramine

A double-blind study compared the efficacy of *H. perforatum* and imipramine in 135 patients diagnosed with depression. The analysis of Clinical Global Impressions revealed comparable results in both treatment groups. Like the comparative study of *H. perforatum* extract vs maprotiline, fewer side effects were found in comparison to imipramine (Vorbach et al. 1994) (Fig. 3.23).

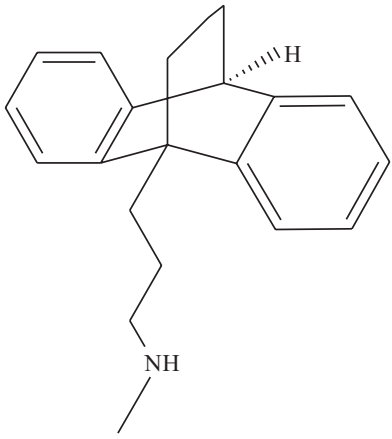


Fig. 3.21 Structure of maprotiline

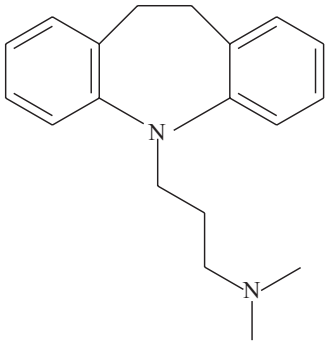


Fig. 3.22 Structure of imipramine

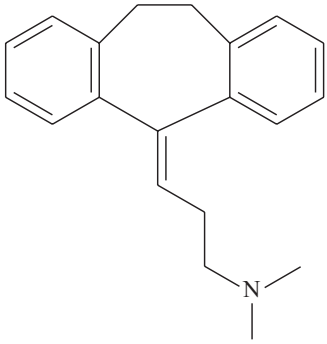


Fig. 3.23 Structure of amitriptyline

3.13.4.3 *Hypericum* Extract Versus Amitriptyline

A controlled, randomized, multicentre trial investigated antidepressant activities of *H. perforatum* and amitriptyline (75 mg). In a trial lasting for 6 weeks, *H. perforatum* (900 mg daily in divided doses) was well tolerated as compared to amitriptyline. Further, in *H. perforatum* group, 37% of patients experienced side effect events in comparison to 64% in the group receiving amitriptyline (Wheatley 1997).

3.13.4.4 *Hypericum* Extract Versus Fluoxetine

A randomized, double-blind study concluded that both *H. perforatum* extract and fluoxetine were having equally potent antidepressant activity. *H. perforatum* was superior to fluoxetine in improving the responder rate and in terms of overall incidence of side effects (Schrader 2000) (Fig. 3.24).

3.13.4.5 *Hypericum* Extract Versus Sertraline

A double-blind, multicentre clinical study proved *H. perforatum* extract was not inferior to sertraline. Further, the extract was well tolerated when treating moderate depression. *H. perforatum* extract yielded these results with a dose of 612 mg once daily up to 6 months (Gastpar et al. 2005) (Fig. 3.25).

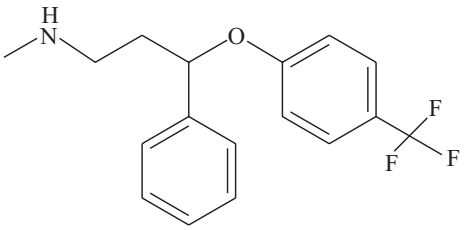


Fig. 3.24 Structure of fluoxetine

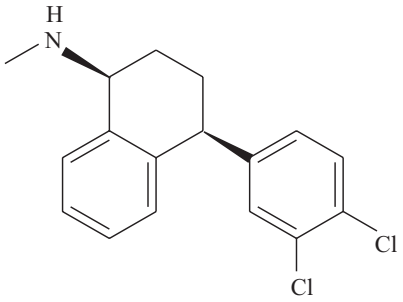


Fig. 3.25 Structure of sertraline

3.13.4.6 *Hypericum* Extract Versus Citalopram

A double-blind, randomized, multicentre, placebo-controlled study confirmed the non-inferiority of *H. perforatum* extract in comparison to citalopram. The superiority of both was demonstrated as compared to the placebo. *H. perforatum* extract proved to be more safe and tolerable as compared to citalopram (Gastpar et al. 2006) (Figs. 3.26 and 3.27).

3.13.4.7 *Hypericum* Extract Versus Paroxetine

A subgroup analysis in moderate major depressive episode showed that patients treated with *H. perforatum* extract showed a reduction in depression severity score. Greater response and remission rates were evident in *H. perforatum* extract in comparison to patients who received paroxetine (Seifritz et al. 2016).

3.14 Neuropharmacology of Other Hypericum Species

3.14.1 *Hypericum calycinum* L.

The plant is commonly known as Great St John's wort. The extract prepared from *H. calycinum* was found to be equally effective as desipramine and trimipramine in animal models (Öztürk et al. 1996).

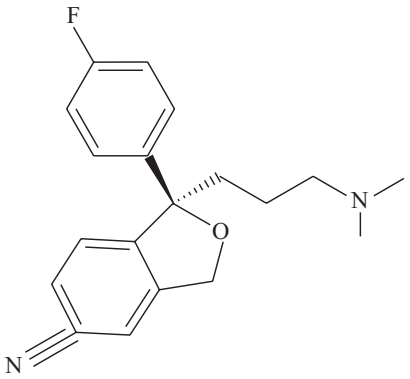


Fig. 3.26 Structure of citalopram

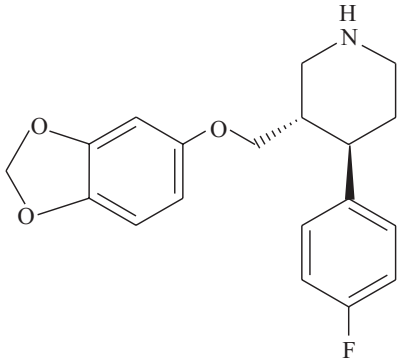


Fig. 3.27 Structure of paroxetine

3.14.2 *Hypericum caprifoliatum* Cham. & Schltdl.

A fraction obtained from the plant rich in phloroglucinol derivatives demonstrated antidepressant-like effect on forced swimming test. Antidepressant-like effect might be related to inhibitory effect on sodium influx (Centurião et al. 2014).

3.14.3 *Hypericum connatum* Lam.

H. connatum Lam. is native to South America. It showed protective activity in the escape deficit test, a correlate of potential antidepressant-like effects that appeared to be related to the flavonoids including quercetin, isoquercitrin and rutin (Scheggi et al. 2016).

3.14.4 *Hypericum elegans* Willd.

In folk medicine of Bulgaria, the plant is used in the treatment of depression. Benzophenones (elegaphenone and 7-epiclusianone) have been reported to have acetylcholinesterase inhibitory activity (Zheleva-Dimitrova et al. 2013).

3.14.5 *Hypericum enshiense* L. H. Wu et F. S. Wang

This plant is native to China. The hydroalcoholic extract significantly shortened the immobility time in forced swimming test and tail suspension test demonstrating potential antidepressant-like activity in the animal behavioural models (Wang et al. 2010a).

3.14.6 *Hypericum grandifolium* Choisy

H. grandifolium is found in the Canary Islands. The butanol and chloroform fractions and all subfractions demonstrated an antidepressant effect in the forced swimming test. The chloroform fraction was found to be most active (Sánchez-Mateo et al. 2009).

3.14.7 *Hypericum hookerianum* Wight & Arn.

Hooker's St John's wort grows in the Nilgiris. In an investigatory study, 200 and 400 mg/kg, p.o., of the *H. hookerianum* extract resulted in enhancement in spontaneous motor activity in mice. Further, the extract significantly reduced the pentobarbitone-induced sleeping time in mice (Mukherjee et al. 2001).

3.14.8 *Hypericum montbretti* Spach.

Rutin and quercitrin are the chief phenolic compounds present in the plant. The extract at 100 and 250 mg kg showed a dose-dependent antidepressant activity (Can et al. 2011a). Methanolic extract has significant anticonvulsant and sedative activities as evident from reduction in spontaneous locomotory activity, potentiation of hexobarbital-induced sleeping parameters and prevention of pentylenetetrazole-induced seizures in comparison to the controls (Can and Ozkay 2012).

3.14.9 *Hypericum mysorense* B.Heyne

The plant is found in Western Ghats. It is used in the treatment of depression (Shanmugam and Shanmugasundaram 2009).

3.14.10 *Hypericum origanifolium* Willd.

Chlorogenic acid and rutin are the chief phenolic compounds present in the plant. The *H. origanifolium* extract demonstrated potential antidepressant, anxiolytic and antinociceptive activities after acute administrations. The CNS effects are probably mediated through via GABAergic and opioidergic mechanisms (Yaşar et al. 2013).

3.14.11 *Hypericum patulum* Thunb.

Goldencup St John's wort grows in the Nilgiris. In an investigatory study, 200 and 400 mg/kg, p.o., of the *H. hookerianum* extract enhanced the spontaneous motor activity in mice. The extract significantly reduced the pentobarbitone-induced sleeping time in mice (Mukherjee et al. 2001).

3.14.12 *Hypericum reflexum* L. fil.

In the forced swimming test, the butanol and chloroform fractions of the methanolic extract resulted in a significant reduction of the immobility time (Sánchez-Mateo et al. 2007).

3.15 *H. perforatum* and Attention-Deficit Hyperactivity Disorder (ADHD)

An open-label pilot study reported that utility of *H. perforatum* reported effectiveness in the treatment of major depressive disorder among youths (Findling et al. 2003).

A study reported that *H. perforatum* has potential to diminish the efficacy of methylphenidate in treating patients diagnosed with attention-deficit hyperactivity disorder (Niederhofer 2007) (Fig. 3.28).

The children aged 6 to 17 years with attention-deficit hyperactivity disorder were assigned to consume 300 mg of an extract of *H. perforatum* standardized to 0.3 % hypericin or placebo, thrice a day for a period of 2 months. An improvement was noticed in both *H. perforatum*- and placebo-treated groups. However, *H. perforatum* failed to offer any additional benefit (Weber et al. 2008).

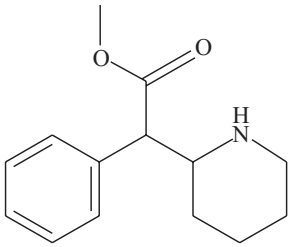


Fig. 3.28 Structure of methylphenidate, a CNS stimulant

An open trial exploring utility of *H. perforatum* in the treatment of patients with autism reported modestly effectiveness in the short-term management of irritability in few patients (Niederhofer 2009).

In an open trial, *H. perforatum* or a placebo was tested in three 14–16-year-old male psychiatric outpatients diagnosed with attention-deficit hyperactivity disorder. The Conner's Scale and Continuous Performance Test were employed for measuring the efficacy of the herbal drug. *H. perforatum* was shown to be slightly effective treatment for attention-deficit hyperactivity disorder (Niederhofer 2010).

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Neuropharmacology of Lavender, Rosemary and Salvia

4

4.1 *Lavandula officinalis* Chaix ex Vill.

4.1.1 Synonyms: *L. angustifolia* Mill., *L. pyrenaica* DC. and *L .vera* DC.

4.1.2 Introduction

English lavender and true lavender are common names of *L. officinalis.* The plant belongs to the family Lamiaceae and is native to the Mediterranean.

4.1.3 Botany

English lavender is a shrub having strong odour and grows up to 1–2 metres high. The leaves of the plant are evergreen, 2–6 centimetres in length and 4–6 millimetres in breadth. The flowers are pinkish-purple in colour and produced spikes 2–8 centimetres long at the top of its slender, leafless stem that is also 10–30 centimetres long.

4.1.4 Chemistry

The essential oil contains 1,8-cineole, 3-octanone, camphor, caryophyllene, cis-ocimene, lavandulyl acetate, limonene, linalool, linalyl acetate, terpinen-4-ol, trans-ocimene and α-pinene.

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_4

4.1.5 Neuropharmacology

4.1.5.1 Preclinical

Neurodepressive

Swiss mice were administered orally with essential oil of lavender at 1/60 in olive oil. In animal models of hole board test, four plate test and plus-maze test, sedative activity was observed. A potentiation of barbiturate sleeping time was also noticed. A potential interaction was supposed to exist as evident by increase in sleeping time and shortening of asleeping time (Guillemain et al. 1989).

Antidepressant and Anxiolytic

In mice, essential oil of lavender exhibited an anxiolytic effect, and the pentobarbital evokated sleeping time was increased in animals, but this effect disappeared if animals were administered for 5 days (Delaveau et al. 1989).

The extract of *L. officinalis* was investigated in scopolamine-induced memory impairment and anxiety- and depression-like behaviour. The hydroalcoholic extract of aerial parts of *L. officinalis* improved scopolamine-induced memory impairment and also reduced anxiety- and depression-like behaviour in a dose-dependent fashion (Rahmati et al. 2017).

4.1.5.2 Clinical

Anxiety

A study was undertaken to compare the anxiolytic effects of a commercial preparation of capsule containing lavender oil with placebo in primary care. The commercial preparation demonstrated potential benefit on the duration and quality of sleep. It also resulted in an improvement in body health and mind. No side effect was observed (Kasper et al. 2010).

A multicentre, double-blind, randomized study involving adults with generalized anxiety disorder demonstrated that a commercial preparation of capsule containing lavender oil was as equally effective as lorazepam. The commercial preparation was also safe (Woelk and Schläfke 2010) (Fig. 4.1).

A comparative study investigated the anxiolytic activity of anxiolytic efficacy of commercial preparation of capsule containing lavender oil and placebo and paroxetine. The commercial preparation demonstrated a striking antidepressant effect. It also resulted in an improvement in general health issues (Kasper et al. 2014) (Fig. 4.2).

Depression

A comparative double-blind study investigated the efficacy of tincture of *L.angustifolia* and imipramine in the treatment of mild to moderate depression in 45 patients. The combination of both was reported to be more effective as compared to imipramine alone (Jashmidi et al. 2003) (Fig. 4.3).

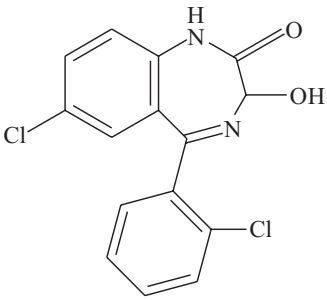


Fig. 4.1 Structure of lorazepam

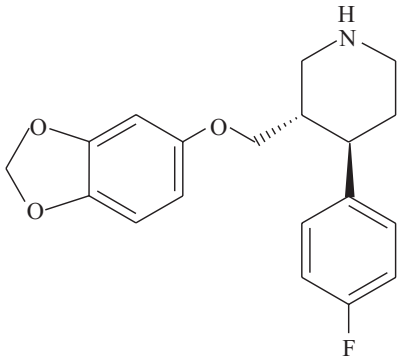


Fig. 4.2 Structure of paroxetine

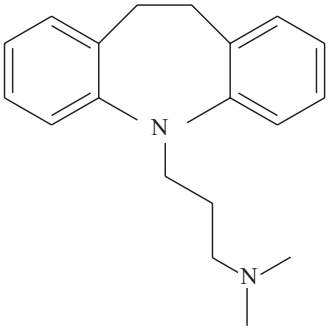


Fig 4.3 Structure of imipramine

A randomized, single-blind study evaluated aromatherapy with *L. angustifolia* as a possible treatment for mild insomnia, and beneficial effect was reported (Lewith et al. 2005). According to another study, aromatherapy with *L. angustifolia* demonstrated a positive impact on insomnia and depression in female college students (Lee and Lee 2006).

A study investigated the effect of an infusion of *L. angustifolia* in the treatment of depressive patients in consuming citalopram. The infusion decreased mean depression score. It was concluded that the infusion alone in combination with antidepressants may be helpful to treat depression (Nikfarjam et al. 2013) (Fig. 4.4).

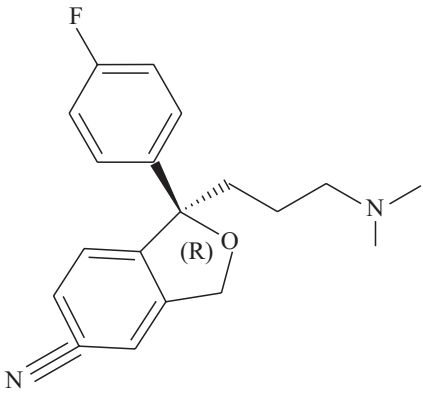


Fig 4.4 Structure of citalopram

4.2 *Rosmarinus officinalis* L.

4.2.1 Introduction

R.officinalis is commonly known as rosemary and belongs to the family Lamiaceae (Mint family). *R.officinalis* is native to Asia and the Mediterranean.

4.2.2 Botany

R.officinalis is an aromatic evergreen shrub. The plant cane is found upright or trailing. The upright one grows 1.5 m tall. The evergreen leaves have a length of 2–4 cm and breadth of 2–5 mm. The upper surface of the leaves is green and the lower surface is white. The flowers are deep blue, pink, purple or white in colour.

4.2.3 Actions

Memory enhancer (nootropic) and stimulant.

4.2.4 Chemistry

Betulinic acid, caffeic acid, camphor (10–20%), carnosic acid, carnosol, rosmarinic acid and ursolic acid (Figs. 4.5, 4.6, 4.7, and 4.8).

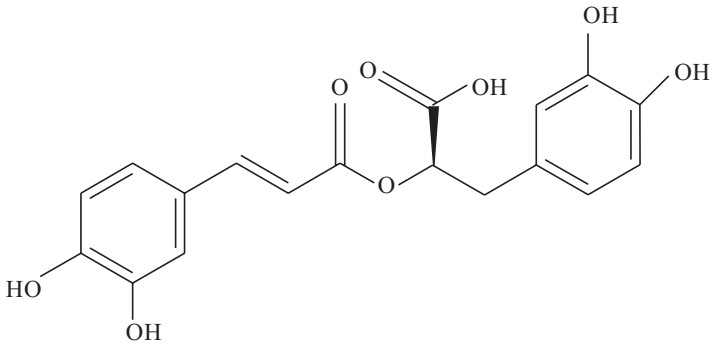


Fig 4.5 Structure of rosmarinic acid

Fig 4.6 Structure of ursolic acid

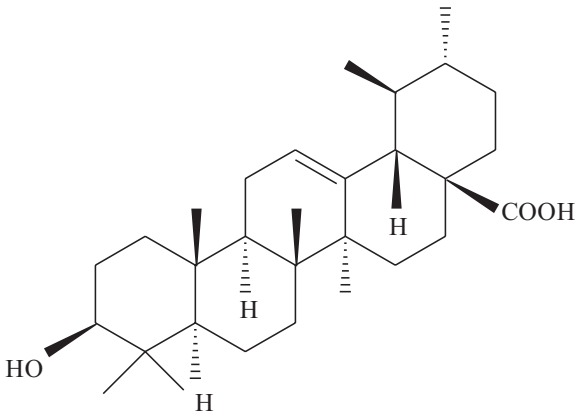
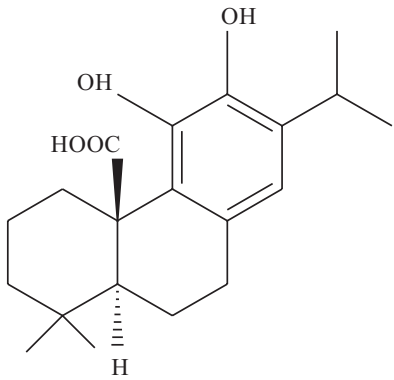


Fig 4.7 Structure of carnosic acid



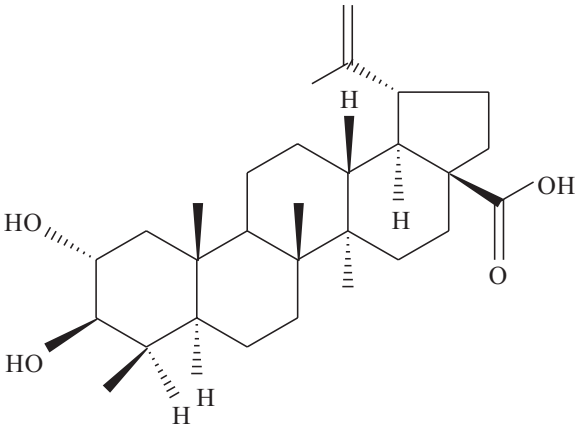


Fig 4.8 Structure of betulinic acid

4.2.5 Neuropharmacology

4.2.5.1 Preclinical

Antidepressant and Anxiolytic

Three compounds (cirsimaritin, rosmanol and salvigenin) demonstrated central nervous system stimulant activity in animal models of antidepressant, anti-anxiety and antinociception. Pentylenetetrazol resulted in inhibition of anti-anxiety activity of three compounds. Involvement of GABAA receptors has been explained as a possible mode of action for inhibition (Akhondzadeh et al. 2015) (Figs. 4.9, 4.10, and 4.11).

Antiepileptic

Ten animals were pretreated with percolated extract of *R. officinalis* in doses of 50, 200, 500 and 1000 mg kg^{-1} and soxhelet extract of *R. officinalis* in doses of 50 and 100 mg kg^{-1} via intraperitoneal injection. After a time period of 20 min, the animals were administered with picrotoxin in a dose of 12 mg kg^{-1} for induction of seizures. It was concluded that *R. officinalis* extract possess anticonvulsant activity against seizures induced by picrotoxin in animals (Heidari et al. 2005).

Antiparkinson's

A study investigated efficacy of carnosol on rotenone-induced neurotoxicity in cultured dopaminergic cells. The compound significantly improved the cell viability via downregulation of caspase-3. Carnosol also resulted in significant increase in extracellular signal-regulated kinase ½, Nurr 1 and tyrosine (Kim et al. 2006) (Fig. 4.12).

Neuroprotective

The hydroalcoholic leaf extract of *R. officinalis* was studied for the ischemic tolerance effect. The animals were divided into two groups, sham group (subjected to surgery without MCAO (middle cerebral artery occlusion) and MCAO group. Oral

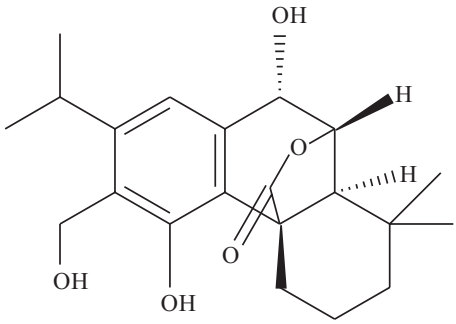


Fig 4.9 Structure of rosmanol

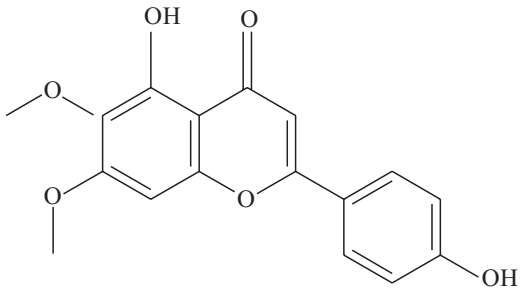


Fig 4.10 Structure of cirsimaritin

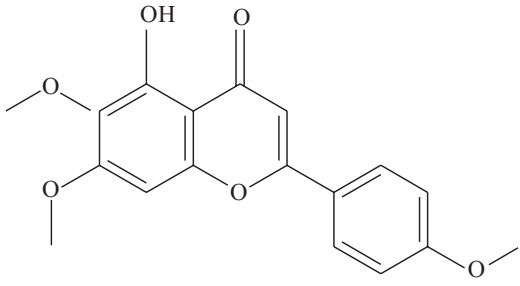


Fig 4.11 Structure of salvigenin

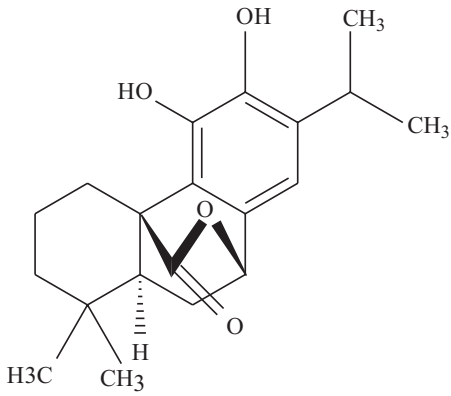


Fig 4.12 Structure of carnosol

pretreatment with different doses (50, 75 and 100 mg/Kg/day) of the hydroalcoholic leaf extract of *R. officinalis* offered a potential role in tolerance against cerebral ischemia-reperfusion injury (Seyedemadi et al. 2016).

4.3 *Salvia officinalis* L.

4.3.1 Introduction

S. officinalis is addressed by several names including common sage, culinary sage or garden sage. The plant is a member of the family Lamiaceae. *S. officinalis* is native to the Mediterranean but has naturalized throughout the world.

4.3.2 Botany

S. officinalis is an evergreen perennial shrub growing to a height of 2 feet. The tap root system is strong with square woody stems. The leaves are toothed, elliptical and hairy. The flowers are violet-blue in colour.

4.3.3 Chemistry

The leaves contain caffeic acid, carnosic acid, carnosol, chlorogenic acid, fumaric acid, ursolic acid and ursonic acid. The essential oil contains borneol, cineole and thujone (Figs. 4.13, 4.14, 4.15, and 4.16).

4.3.4 Preclinical Neuropharmacology

4.3.4.1 In Vitro Affinity to Human Brain Benzodiazepine Receptor

The flavones, namely, apigenin, cirsimaritin and hispidulin, resulted in a competitive inhibition of 3H-flumazenil binding to the benzodiazepine receptor with IC50 values of 30, 1.3 and 350 microM, respectively. The IC50 value for 7-methoxyrosmanol was 7.2 microM. The IC50 value for a diterpene, galdosol, was 0.8 microM, which was fairly strong (Kavvadias et al. 2003) (Figs. 4.17, 4.18, and 4.19).

4.3.5 Clinical Neuropharmacology

4.3.5.1 Mild to Moderate Alzheimer's Disease

A double-blind and placebo-controlled clinical study reported efficacy of an extract of *S. officinalis* in patients suffering from mild to moderate Alzheimer's disease. After 4 months of treatment, the extract showed a potential effect on cognitive functions as compared to placebo. The extract reduced the incidence of agitation among the patients (Akhondzadeh et al. 2003).

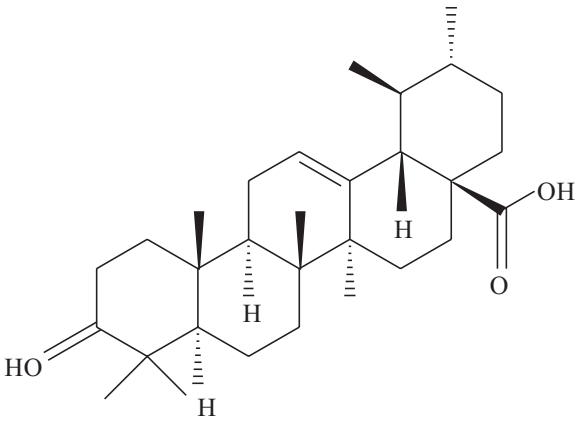


Fig 4.13 Structure of ursonic acid

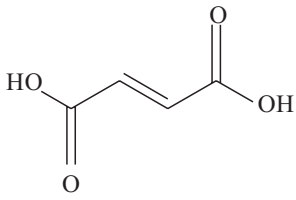


Fig 4.14 Structure of fumaric acid (*trans*-butenedioic acid)

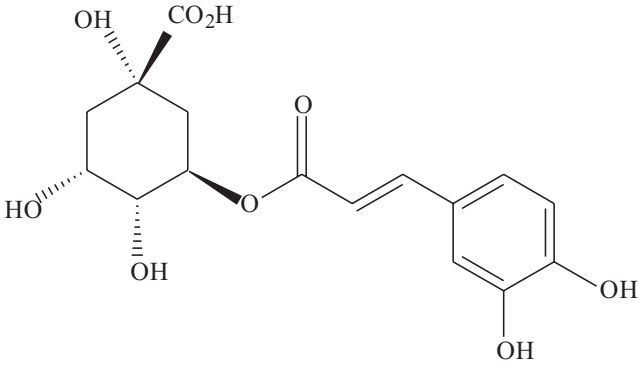


Fig 4.15 Structure of chlorogenic acid

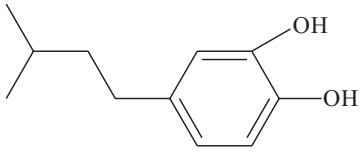


Fig 4.16 Structure of caffeic acid

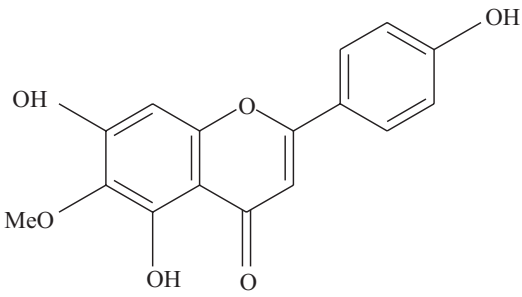


Fig 4.17 Structure of hispidulin

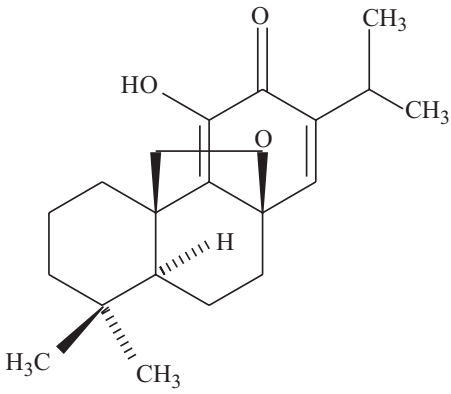


Fig 4.18 Structure of 7-methoxyrosmanol

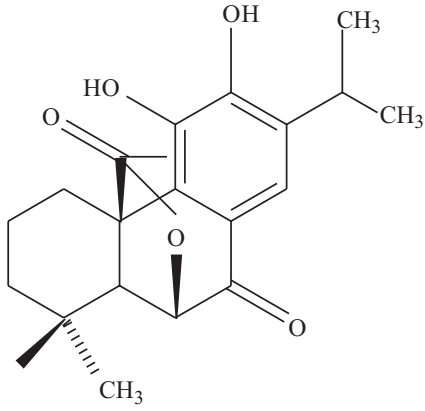


Fig 4.19 Structure of galdosol

4.4 *Salvia lavandulifolia* Vahl

4.4.1 Introduction

S. lavandulifolia is commonly known as Spanish sage. The plant is native to South France and Spain.

4.4.2 Botany

S. lavandulifolia is a small woody perennial herb. The leaves are whitish-gray in colour and lanceolate. The pale flowers are borne on short inflorescence.

4.4.3 Chemistry

Essential oil contains monoterpenes (1,8-cineole, α-pinene, camphor, geraniol, linalool and ϒ-terpinene).

4.4.4 Preclinical Neuropharmacology

4.4.4.1 Acetylcholinesterase Inhibition

The essential oil of *S. lavandulifolia* demonstrated a selective inhibitory effect on acetylcholinesterase (IC50 value of 0.03 μg/ml). IC50 values for 1,8-cineole and α-pinene were 0.67 and 0.63 mM, respectively, and they were regarded as active constituents. Camphor, geraniol, linalool and ϒ-terpinene were regarded as less potent (Perry et al. 2000) (Figs. 4.20 and 4.21).

4.4.5 Clinical Neuropharmacology

In the first trial, 20 participants were assigned to receive doses of 50, 100 and 150 μl of a standardized essential oil of Spanish sage and placebo. In the second trial, 24 participants were assigned to receive doses of 25 and 50 μl of a standardized essential oil of Spanish sage and placebo. The 50 μl dose was found to be effective in both the trials in improving the recalling of the words (Tildesley et al. 2003).

4.5 *Salvia verticillata* L.

S. verticillata is commonly known as lilac sage or whorled clary. Lilac sage is native to Central Europe and Western Asia. Now, the plant has widely naturalized in North America and North Europe.

4.5.1 Botany

S. verticillata is a perennial plant. The mid-green leaves are simple and are covered with hairs. The leaf-covered stems have inflorescence growing up to 3 feet. Lilac blue flowers are found in terminal racemes.

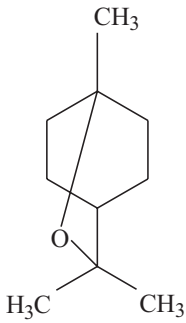


Fig 4.20 Structure of 1,8-cineole

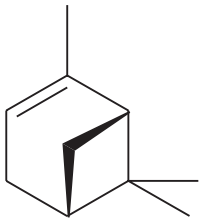


Fig 4.21 Structure of α-pinene

4.5.2 Chemistry: Rosmarinic Acid

4.5.3 Preclinical Neuropharmacology

4.5.3.1 Anticonvulsant and Antidepressant

The hydroalcoholic extract of *S. verticillata* resulted in a significant anticonvulsant activity in maximal electroshock- and pentylenetetrazol-induced seizures. In the case of tests related to depression (forced swim test and tail suspension test), the hydroalcoholic extract of *S. verticillata* resulted in a significant antidepressant effect in mice as compared to the control group (Naderi et al. 2011).

4.6 *Salvia elegans* Vahl

S. elegans is commonly called pineapple sage or tangerine sage. It is native to Mexico and Guatemala.

4.6.1 Botany: *S. elegans* is a perennial Shrub

4.6.2 Chemistry

Caffeic acid derivatives, lithospermic acid B, lithospermic acid and flavone luteolin-O-glucuronide (Figs. 4.22 and 4.23).

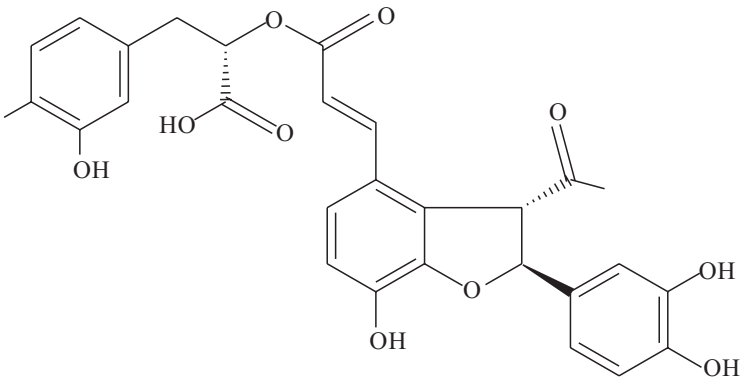


Fig 4.22 Structure of lithospermic acid

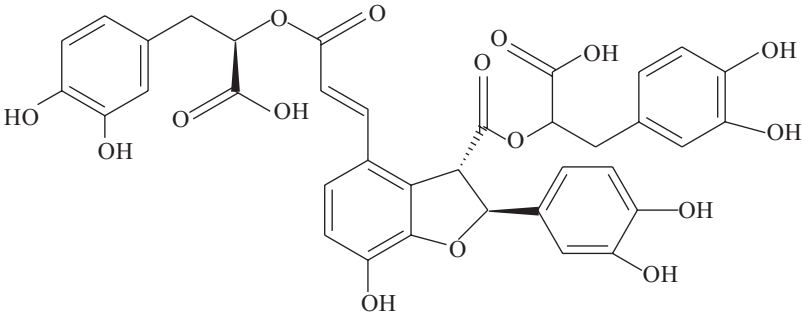


Fig 4.23 Structure of lithospermic acid B

4.6.3 Traditional Medicinal Use

S. elegans is used in Mexican traditional medicine for the treatment of an array of diseases related to the central nervous system including anxiety neurosis (Herrera-Ruiz et al. 2006).

4.6.4 Preclinical Neuropharmacology

4.6.4.1 Antidepressant and Anxiolytic

In elevated maze test, the hydroalcoholic extract of *S. elegans* on oral administration resulted in an increase in the percentage of time spent and arm entries in the open arms. The extract also increased the time spent by animals in the illuminated side of the light-dark test. In the forced swimming test, the hydroalcoholic extract of *S. elegans* decreased the immobility time of mice (Herrera-Ruiz et al. 2006).

4.7 *Salvia reuterana* Boiss

4.7.1 Botany

S. reuterana is a perennial shrub.

4.7.2 Chemistry

Labdane diterpenoids (Farimani and Miran 2014) and essential oil contain (E)-β-ocimene (32.3%), germacrene-D (11.2%), hexyl acetate (7.6%) and α-gurjunene (14.1%) (Mirza and Sefidkon 1999).

4.7.3 Traditional Medicinal Use

S. reuterana is used in Iranian traditional medicine for curing insomnia.

4.7.4 Preclinical Neuropharmacology

4.7.4.1 Anti-anxiety

In elevated maze test, the hydroalcoholic extract of *S. reuterana* in a dose of 100 mg/kg resulted in an increase in the percentage of time spent and arm entries in the open arms. In animals pretreated with diazepam and hydroalcoholic extract of *S. reuterana*, the measurement of spontaneous locomotor activity count in 15 min was decreased in a significant fashion (Rabbani et al. 2005).

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Neuropharmacology of *Passiflora* Genus

5

5.1 *Passiflora incarnata* L.

P. incarnata is addressed by several names like maypop, purple passionflower, true passionflower, wild apricot and wild passion vine and is a member of family Passifloraceae. *P. incarnata* is common to the southeast United States. The dried herb is used in medicine and collected after some of the berries have matured.

5.2 Botany

P. incarnata is a perennial herb. The stems can vary from smooth to pubescent, long, trailing and have many tendrils. The leaves are alternate and palmately three lobed. They measure 6–15 cm and possess two glands on the petiole. The five petals of the flower bluish-white in colour. Fleshy, egg-shaped, edible fruits called maypops appear in July and mature to a yellowish colour in fall (Brasseur and Angenot 1984; Dhawan et al. 2001a, 2004; Hans et al. 2010).

5.3 Phytochemistry (Fellows and Smith 1938)

5.3.1 Flavonoids (2.5%) (Gavaseli 1970; Menghini and Mancini 1988; Schmidt and Ortega 1993; Rehwald et al. 1994)

Flavone di-C-glycosides: shaftoside, isoshaftoside, isovitexin, 7 isoorientin, vicenin, lucenin, saponarin and passiflorine (Li et al. 1991) (Figs. 5.1, 5.2, 5.3, 5.4, 5.5 and 5.6)

Free flavonoids include apigenin, luteolin, quercetin and kaempferol.

The total flavonoid content of the leaves of *P. incarnata* before flowering was 0.22%, and that of the roots was 0.35%. During flowering the content of the leaves was 0.31, of the flowers 0.23 and of the roots 0.21%. At the start of fruiting, the

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_5

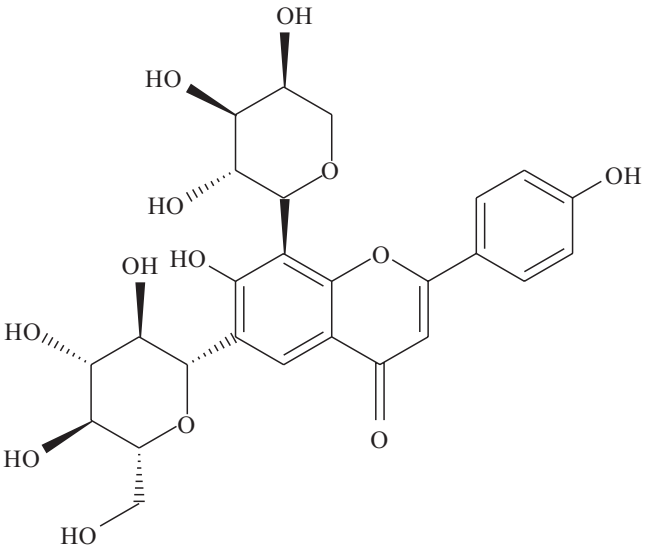


Fig. 5.1 Chemical structure of shaftoside

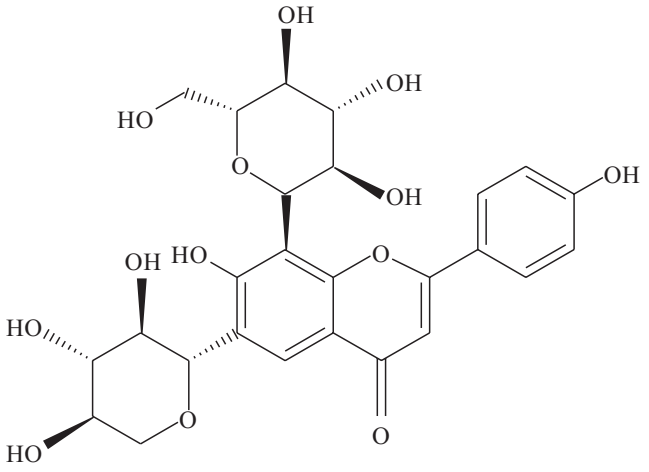


Fig. 5.2 Chemical structure of isoshaftoside

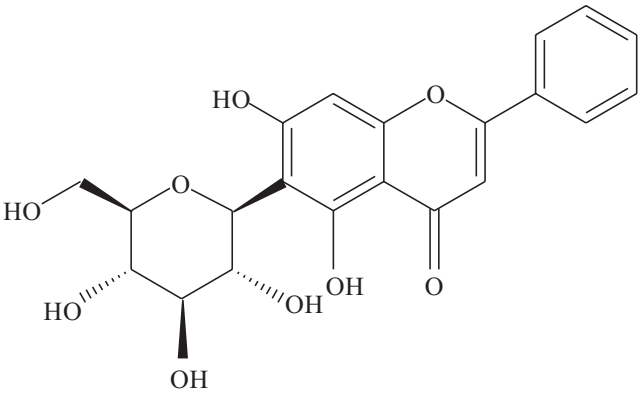


Fig. 5.3 Chemical structure of isovitexin

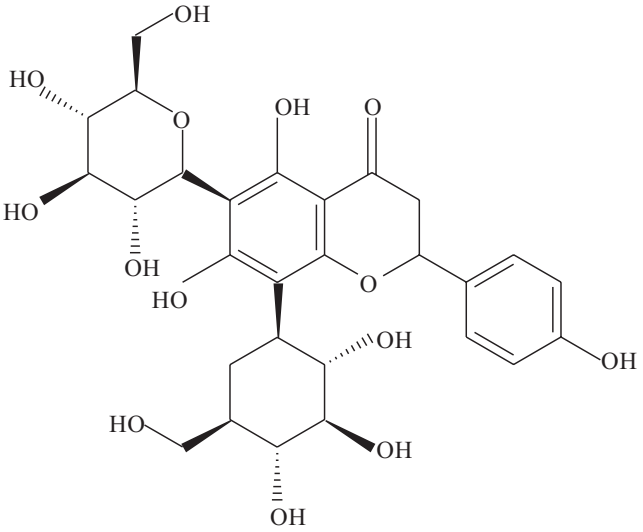


Fig. 5.4 Chemical structure of vicenin

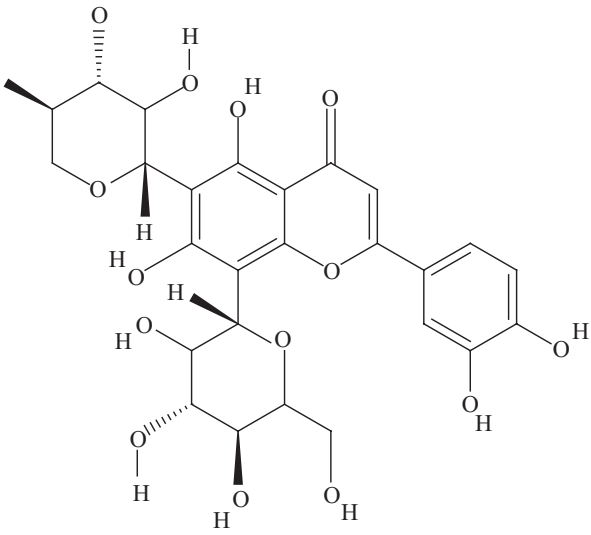


Fig. 5.5 Chemical structure of lucenin 1

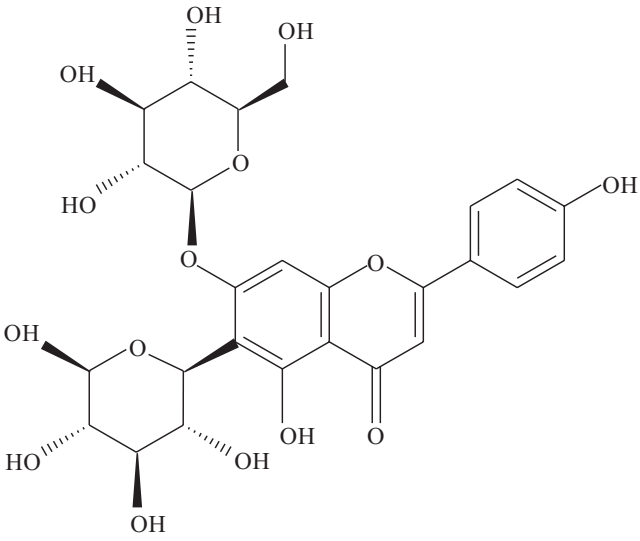


Fig. 5.6 Chemical structure of saponarin

leaves contained 0.15 and the roots 0. 13%. Paper chromatography confirmed the presence of rutin (Rt 0.53), quercetin (Rf 0.7) and an unidentified flavonoid (Gavaseli 1978).

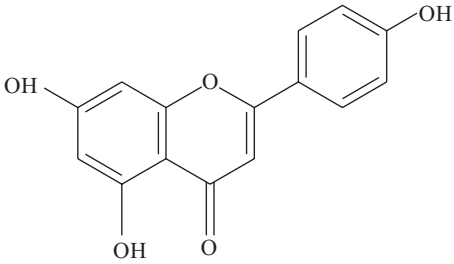


Fig. 5.7 Chemical structure of apigenin

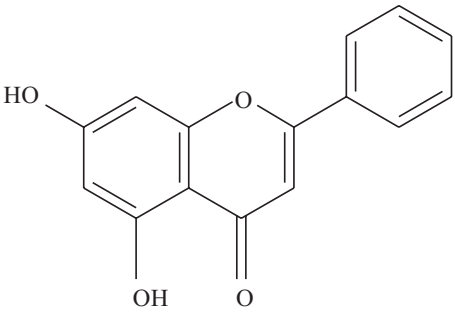


Fig. 5.8 Chemical structure of chrysin

5.3.1.1 Apigenin (Fig. 5.7)

5.3.1.2 Chrysin (Figs. 5.8, 5.9, 5.10 and 5.11)

5.3.2 Alkaloids

Harmol, harman, harmine and harmalol (Bennati 1971) (Figs. 5.12, 5.13, 5.14 and 5.15)

5.3.3 Glycoside

Passiflorine

5.3.4 Organic Compounds

Maltol (Aoyagi et al. 1974) (Fig. 5.16)
Ethyl maltol (Aoyagi et al. 1974) (Fig. 5.17)

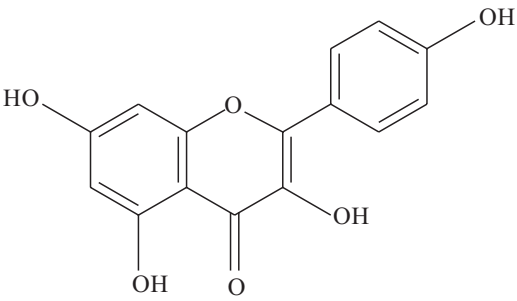


Fig. 5.9 Chemical structure of kaempferol

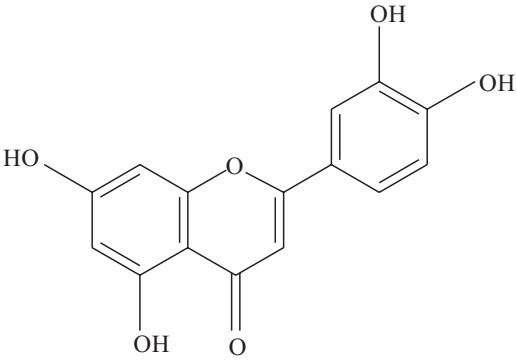


Fig. 5.10 Chemical structure of luteolin

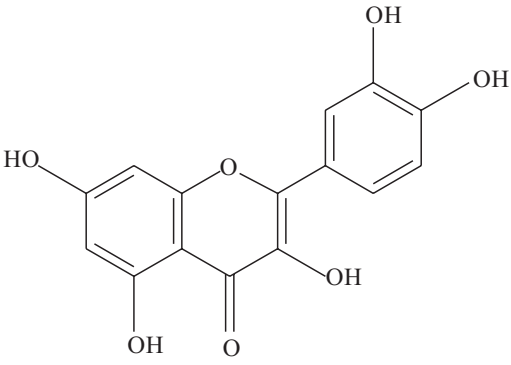


Fig. 5.11 Chemical structure of quercetin

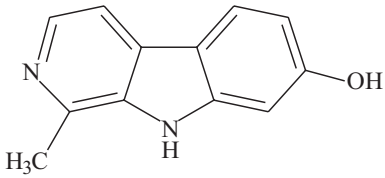


Fig. 5.12 Chemical structure of harmol

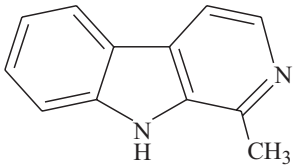


Fig. 5.13 Chemical structure of harman

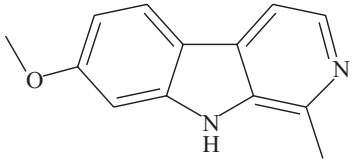


Fig. 5.14 Chemical structure of harmine

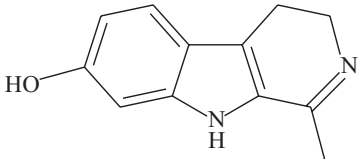


Fig. 5.15 Chemical structure of harmalol

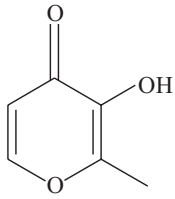


Fig. 5.16 Chemical structure of maltol

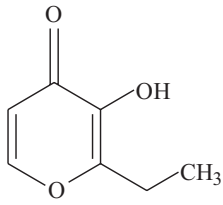


Fig. 5.17 Chemical structure of ethyl maltol

5.3.5 Alkaloid

3-methyl-4-carbolin (2′-methyl-(pyridino-3′, 4′: 2,3-indole)) (Neu 1956)

5.3.5.1 Actions

Antianxiety, hypnotic, analgesic, antispasmodic, antiasthmatic, vermicidal and sedative (Patel et al. 2009)

5.3.5.2 Therapeutics

The Native Americans more so than any other tribal cultures have used the dried leaves of the plant as a primary ingredient in the creation of a special tisane that is drunk to help treat insomnia, epilepsy, anxiety, hysteria and some types of mania and hyperactivity.

In Europe, *P. incarnata* is used in the treatment of anxiety and insomnia. In Brazil, the plant is used as analgesic, antiasthmatic, antispasmodic, sedative and vermicidal. In Iraq, the plant is reputed remedy as narcotic and sedative. In Turkey, *P. incarnata* is used in the treatment of dysmenorrhoea, epilepsy, insomnia, neurosis and neuralgia.

Polish people use *P. incarnata* in the treatment of neurasthenia and hysteria. In the United States, *P. incarnata* is used in the treatment of burns, diarrhoea, dysmenorrhoea, haemorrhoids, insomnia and neuralgia. The plant is a valued remedy for the treatment of opium dependence in India (Krenn 2002; Patel et al. 2009; Miroddi et al. 2013).

5.4 Preclinical Neuropharmacology

5.4.1 Antianxiety

Lyophilized aqueous and hydroalcoholic extracts derived from the aerial parts of *P. incarnata* and chemical constituents including indole alkaloids, flavonoids and maltol were investigated for behavioural effects in mice. The hydroalcoholic extract demonstrated antianxiety effect at a dose of 400 mg/kg. The aqueous extract demonstrated sedative effect at a dose of 400 mg/kg and induced sleep in animals treated with pentobarbital (Soulimani et al. 1997) (Fig. 5.18).

In the elevated plus-maze model, the aqueous, chloroform, methanol and petroleum ether extracts of whole part and sorted parts of *P. incarnata* were tested for antianxiety (anxiolytic) activity. The methanol extracts of whole and sorted parts of *P. incarnata* demonstrated anxiolytic effects at doses of 100, 125, 200 and 300 mg/kg, respectively (Dhawan et al. 2001b).

In the elevated plus-maze model, a fraction derived from the methanol extract of *P. incarnata* exhibited potent antianxiety (anxiolytic) activity at a dose of 10 mg (Dhawan et al. 2001c).

In a 7-day chronic regimen, mice in different groups were administered with alcohol, alcohol plus 10, 20 and 50 doses of the benzoflavone moiety of *P. incarnata*

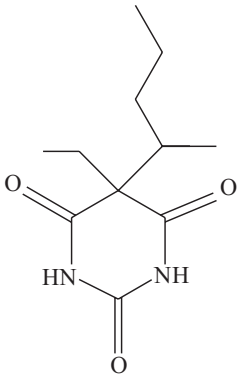


Fig. 5.18 Chemical structure of pentobarbital

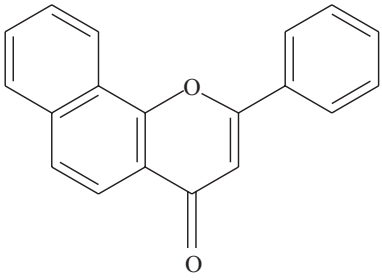


Fig. 5.19 Chemical structure of benzoflavone

and vehicle for 6 days, twice daily. Other three groups of mice were rendered addicted with ethyl alcohol in a dose of 2 g/kg for 6 days, twice daily. These were also administered 10, 20 and 50 doses of the benzoflavone moiety of *P. incarnata* on the seventh day. In both (acute as well as chronic) cases, the benzoflavone moiety significantly prevented the expression of alcohol withdrawal. The benzoflavone moiety also significantly decreased the incidence of anxiety in mice (Dhawan et al. 2002a, b) (Fig. 5.19).

The rats in a double-blind, placebo-controlled study received an i.p. injection of:

A. Vehicle (dimethyl sulfoxide 4%)
B. Chrysin in a dose of 2 mg/kg
C. Midazolam in a dose of 1.5 mg/kg
D. Flumazenil in a dose of 3 mg/kg
E. Chrysin + flumazenil (Figs. 5.20 and 5.21)

As far as levels of catecholamine and corticosterone are concerned, no statistical difference was observed. Midazolam resulted in a significant reduction in anxiety in comparison to control, flumazenil and chrysin, groups. However, no significant difference was observed in the chrysin group (Brown et al. 2007) (Figs. 5.22 and 5.23).

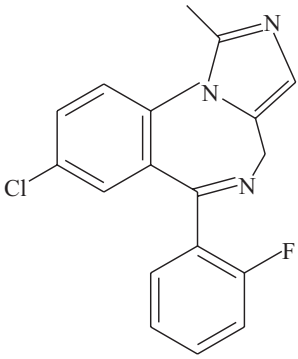


Fig. 5.20 Chemical structure of midazolam

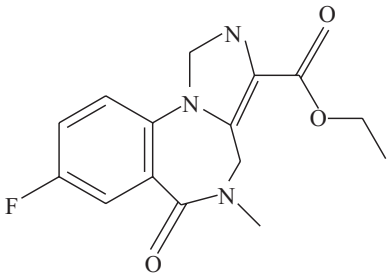


Fig. 5.21 Chemical structure of flumazenil

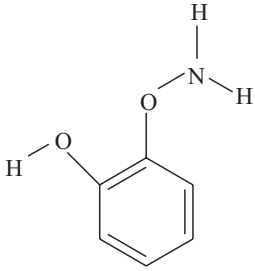


Fig. 5.22 Chemical structure of catecholamine

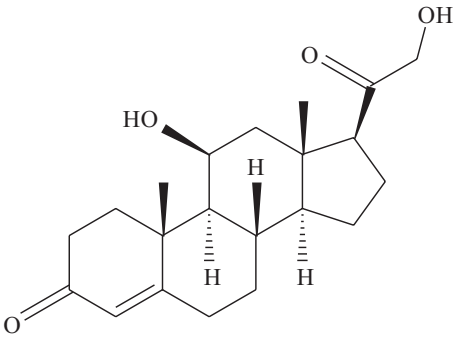


Fig. 5.23 Chemical structure of corticosterone

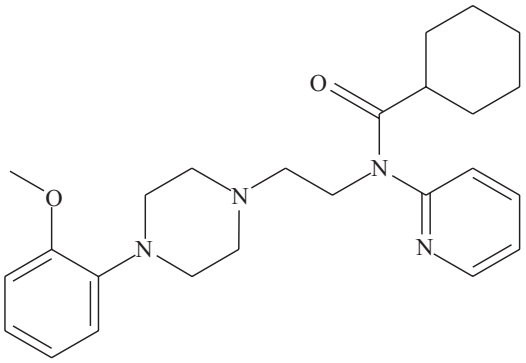


Fig. 5.24 Chemical structure of WAY-100,635 – a piperazine drug

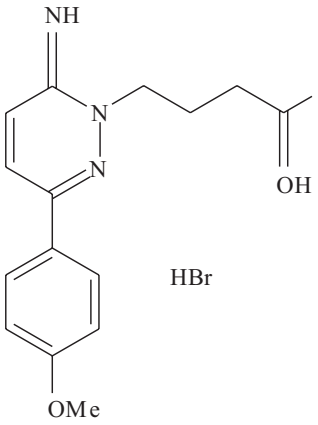


Fig. 5.25 Chemical structure of [(3) H]-SR95531(selective, competitive GABAA receptor antagonist)

The *P. incarnata* extract administered in a dose of 375 mg/kg demonstrated an antianxiety effect comparable to diazepam (1.5 mg/kg). Antagonism studies were conducted utilizing the ϒ-aminobutyric acid (A)/benzodiazepine receptor antagonist flumazenil and the 5-HT (1A)-receptor antagonist WAY-100635. Flumazenil effectively antagonized the active dose, but WAY-100635 failed to do so(Grundmann et al. 2008) (Fig. 5.24).

An in vitro study investigated the effect of dry extract of *P. incarnata* on the ϒ-aminobutyric acid system. The dry extract caused inhibition of [(3) H]-GABA uptake into rat cortical synaptosomes. Further, the extract in a concentration-dependent fashion caused inhibition of the binding [(3) H]-SR95531 to GABAA receptors and of [(3) H]-CGP 54626 to GABAB receptors (Appel et al. 2011) (Figs. 5.25 and 5.26).

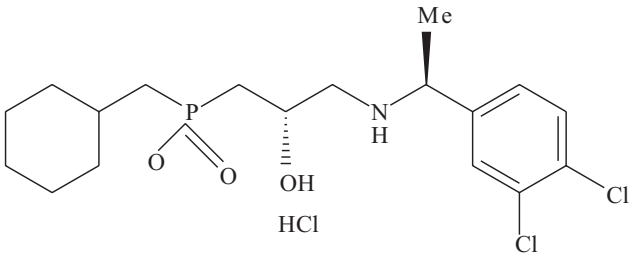


Fig. 5.26 Chemical structure of[(3) H]-CGP 54626(selective, competitive GABAB receptor antagonist)

Fig. 5.27 Chemical structure of pentylenetetrazole

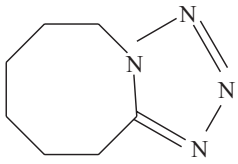
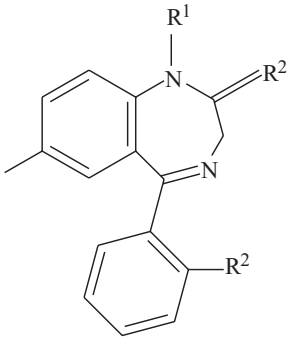


Fig. 5.28 Chemical structure of diazepam



5.4.2 Anticonvulsant

Extracts (five in number) were prepared from a batch of *P. incarnata* and were administered to Charles River mice for 7 days. Two out of the five extracts demonstrated anticonvulsant effect against pentylenetetrazole-induced seizures. All the five extracts demonstrated anxiogenic effects in the elevated plus-maze test in the animals (Elsas et al. 2010) (Fig. 5.27).

Diazepam, normal saline and hydroalcoholic extract of *P. incarnata* were injected i.p. at the doses of 0.4–0.05 mg/kg, 0.5–1 mg/kg and 10 ml/kg, respectively, 30 min before pentylenetetrazole (90 mg/kg, i.p.). The hydroalcoholic extract of *P. incarnata* at a dose of 0.4 mg/kg not only prolonged the onset time of seizure but also decreased the duration of seizure as compared to the saline group (Nassiri-Asl et al. 2007) (Fig. 5.28).

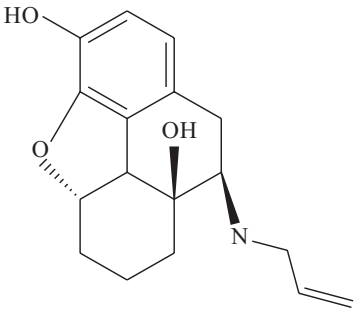


Fig. 5.29 Chemical structure of naloxone

The hydroalcoholic extract of *P. incarnata* was administered in doses of 0.125, 0.25, 0.55 and 1.5 μg by intracerebroventricular injection. The hydroalcoholic extract affected generalized tonic-clonic seizures and minimal clonic seizures induced by pentylenetetrazole (Nassiri-Asl et al. 2008).

The hydro-ethanolic extract of *P. incarnata* suppressed seizures induced by pentylenetetrazole. The extract also ameliorated the postictal depression associated with the convulsant drug. Diazepam has been reported to worsen the incidence of postictal depression (Singh et al. 2012).

5.4.3 Drug/Substance Reversal Effects

The benzoflavone moiety derived from the methanolic extract of *P. incarnata* demonstrated significant antianxiety activity. The extract caused a delay in developing the tolerance to the analgesia of the opium alkaloid, morphine administered in doses of 10, 50 and 100 mg/kg for 9 days. *P. incarnata* in a single dose resulted in a decrease of naloxone-precipitated withdrawal symptoms in mice which have been made tolerant with chronic administration of morphine in a dose of 10 mg/kg (Dhawan et al. 2001d) (Fig. 5.29).

In male rats, *P. incarnata* yielded novel trisubstituted benzoflavone moiety that resulted in prevention of azoospemia, sterility and loss of libido caused by chronic alcohol and nicotine (Dhawan and Sharma 2002). Reversal effects of *P. incarnata* have been reported on nicotine, and the benzoflavone moiety is supposed to be involved (Dhawan et al. 2002a).

A study reported suppressive effect of the benzoflavone moiety *P. incarnata* on alcohol cessation-oriented hyper-anxiety (Dhawan et al. 2002b). As per results of another study, trisubstituted benzoflavone of *P. incarnata* attenuated the benzodiazepine dependence in mice (Dhawan et al. 2003).

5.5 Clinical Neuropharmacology

5.5.1 Anxiety

A study was undertaken on 36 patients with clinical diagnosis of anxiety neurosis using DSM criteria. *P. incarnata* extract and oxazepam (a short- to intermediate-acting benzodiazepine) showed utility in the treatment of generalized anxiety disorder (GAD). No striking difference was noticed between two drugs, but oxazepam has a quick onset of action (Akhondzadeh et al. 2001a, b) (Fig. 5.30).

Sixty patients were randomized in two groups. The first group received *P. incarnata* by oral route in a dose of 500 mg ($n = 30$). The second group received placebo ($n = 30$). Both groups received the drug or placebo as premedication, 90 min before surgical procedure. The numerical rating scales were found to be significantly lower in group receiving *P. incarnata* as compared to placebo (Movafegh et al. 2008).

In a randomized, double-blind and placebo-controlled study, 60 patients (scheduled for spinal anaesthesia) were divided in 2 groups. The first group received *P. incarnata* and the second group received placebo. Preoperative administration of *P. incarnata* by oral route showed suppressive effect on increasing anxiety without disturbing haemodynamics, sedation level and psychomotor functions (Aslanargun et al. 2012).

In a randomized, double-blind, crossover study, 40 participants (bilateral extraction of mandibular third molar was done), *P. incarnata* and midazolam were administered in doses of 260 mg and 15 mg, respectively, prior to surgical procedure. The anxiolytic effect of *P. incarnata* was comparable to midazolam. Further, *P. incarnata* was found to be suitable for sedation in the patients (Dantas et al. 2017) (Fig. 5.31).

5.5.2 Opiates Withdrawal

In a 14-day randomized controlled double-blind study, 65 patients with confirmed history of opium addiction were included. The patients were assigned randomly to consume *Passiflora* extract plus clonidine tablet or clonidine tablet plus placebo drop. Both regimens were found to be equally effective in treatment of the physical

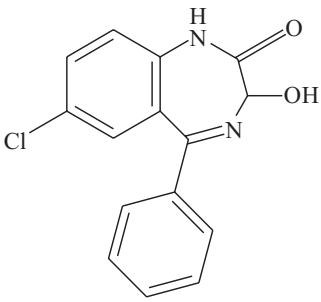


Fig. 5.30 Chemical structure of oxazepam

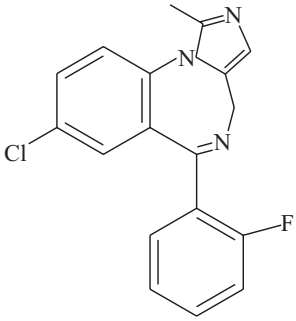


Fig. 5.31 Chemical structure of midazolam

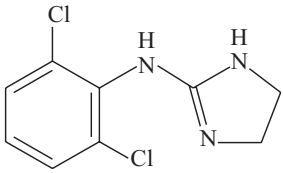


Fig. 5.32 Chemical structure of clonidine

symptoms of withdrawal syndrome. However, the *Passiflora* plus clonidine group was distinctly superior as compared to clonidine as far as treatment of mental symptoms was concerned (Akhondzadeh et al. 2001b) (Fig. 5.32).

5.6 Neuropharmacology of Other *Passiflora* Species

5.6.1 *Passiflora actinia* Hooker

P. actinia is native to Brazil.

5.6.1.1 Botany

P. actinia is an evergreen climber.

5.6.1.2 Preclinical Neuropharmacology

The hydro-ethanolic extract and methanolic extract, crude and chromatographic fractions of *P. actinia* have been reported to induce catalepsy in animals (Santos et al. 2005).

5.6.2 *Passiflora alata* Dryander

The common name for *P. alata* is the winged-stem passionflower. It is native to the Amazon, from Peru to eastern Brazil.

5.6.2.1 Botany

The leaves are oblong or oval. The fragrant flowers are 7–10 cm wide, having curved petals red in colour. The flowers had a prominent fringed corona in bands of purple and white giving the appearance of stripes. The fruit is egg-shaped and yellow to bright orange in colour.

5.6.2.2 Chemistry

Flavonoids including rutin (Pereira and Vilegas 2000) and saponin: quadrangulo-side (Reginatto et al. 2004).

5.6.2.3 Traditional Medicinal Use

P. alata is used in traditional American medicine in the treatment of anxiety neurosis.

5.6.2.4 Preclinical Neuropharmacology

Anxiolytic

Hydro-ethanolic extracts of *P. alata* and *P. edulis* were evaluated for anxiolytic activity in the elevated plus-maze test. Both the extracts demonstrated anxiolytic activity in doses of 50, 100 and 150 mg/kg (Petry et al. 2001).

5.6.3 *Passiflora caerulea* L.

The common names are blue passionflower, bluecrown passionflower or common passionflower. The plant is native to South America.

5.6.3.1 Botany

P. caerulea is a deciduous or semievergreen vine growing up to 1 m. The leaves are palmate and fragrant. The flowers are blue-white in colour having a fringe of coronal filaments in various colours. The fruit is oval in shape and orange in colour. The fruit is edible.

5.6.3.2 Chemistry

Chrysin (Wolfman et al. 1994)

5.6.3.3 Preclinical Neuropharmacology

Anxiolytic

In the elevated plus-maze test of anxiety, diazepam (DZ, 0.3–0.6 mg/kg) and chrysin (1 mg/kg) induced increase in the number of entries into the open arms and in the time spent on the open arms. The effects of chrysin on the elevated plus maze were abolished by pretreatment with the specific BDZ receptor antagonist Ro 15-1788 (3 mg/kg). In the hole board, diazepam (1 mg/kg) and chrysin (3 mg/kg) increased the time spent head-dipping (Wolfman et al. 1994).

5.6.4 *Passiflora edulis* Sims

The common names for *P. edulis* are passion fruit and purple granadilla. It is native to southern Brazil.

5.6.4.1 Botany

P. edulis is a multi-annual evergreen creeper reaching lengths up to 15 m. The stem is rigid, based on dřevnatějící sparsely branched. The base snaps spiral tendrils unbranched. The leaves are alternate, petiolate, blade 3laločná the middle lobe longest, 4–15 cm wide and 5–18 cm long, on the face of the deep to dark green, leathery, glossy. Flowers grow individually from the leaf axils and are 5–9 cm in diameter. The fruits are called passion fruit, rounded, 3–8 cm wide, 4–10 cm long, berries with yellow or purple leathery peel. Inside there is a large amount of seeds surrounded by orange flesh that is very aromatic and has a tart taste.

5.6.4.2 Chemistry

Glycosylflavonoids: vicenin-2, spinosin and 6,8-di-C-glycosylchrysin (Sena et al. 2009), chrysin 6-*C*-*β*-rutinoside, (31R)-31-O-methylpassiflorine and (31S)-31-O-methylpassiflorine, isoorientin and (6S,9R)-roseoside (Zhang et al. 2013)

5.6.4.3 Traditional Medicinal Use

P. edulis is traditionally used in American countries to treat anxiety and nervousness.

5.6.4.4 Preclinical Neuropharmacology

Anxiolytic and Sedative

The aqueous (water) extract of *P. edulis* showed an anxiolytic-like activity, but significant effect on the motor activity was lacking. However, the total flavonoid fraction demonstrated anxiolytic activity and compromisation of the motor activity was noticed. The fractionation of the total flavonoids resulted in isolation and characterization of luteolin-7-O-[2-rhamnosylglucoside]. The compound showed similar activity to the aqueous extract of *P. edulis* (Jun et al. 2010) (Fig. 5.33).

An investigatory study in rats was undertaken to study the central effects of:

A. The aqueous extract
B. The butanolic fraction
C. Aqueous residual fraction, both obtained from pericarp of the *P. edulis flavicarpa* fruit

The aqueous extract, the butanolic fraction and the aqueous residual fraction showed anxiolytic effect as evident from increase in the total time spent in the light compartment of the dark-light box. The aqueous extract showed sedative effect as evident from potentiation of the hypnotic effect of ethyl ether. C-glycosylflavonoids (6,8-di-C-glycosylchrysin, spinosin and vicenin-2) were considered to be active principles (Sena et al. 2009) (Fig. 5.34).

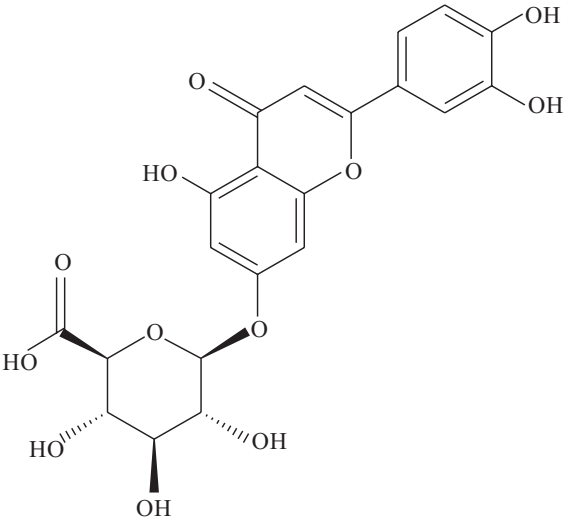


Fig. 5.33 Chemical structure of luteolin-7-O-[2-rhamnosylglucoside]

5.6.5 *Passiflora quadrangularis* L.

P. quadrangularis is commonly known as Giant granadilla.

5.6.5.1 Botany

P. quadrangularis is a rapidly growing herb. The stem is four-angled and thick. The alternate leaves are broad or oblong and cordate at the base. The flowers are aromatic. The fruit is melon like and aromatic also.

5.6.5.2 Chemistry

The root contains an alkaloid passiflora which is identical with harman from *P. incarnata.* The seeds contain a cardiotonic principle.

5.6.5.3 Traditional Medicinal Use

The flesh is used in the treatment of asthma, headache, diarrhoea, dysentery, insomnia and neurasthenia in Brazil.

5.6.5.4 Preclinical Neuropharmacology

Anxiolytic and Sedative

The hydroalcoholic extract of *P. quadrangularis* showed anxiolytic activity in several doses (100, 250 and 500 mg/kg). In plus-maze test, elevation of the time spent on the open arms was the proof for anxiolytic activity. In the open-field test, an increase of deambulation and rearing and decrease of freezing were observed (de Castro et al. 2007).

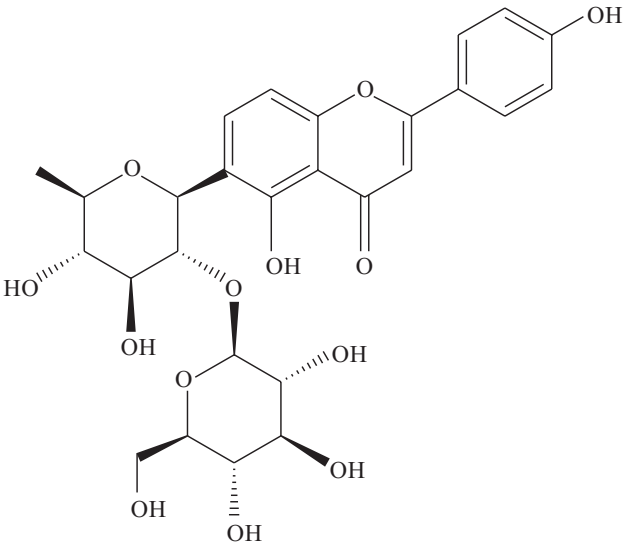


Fig. 5.34 Chemical structure of spinosin

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Neuropharmacology of *Scutellaria baicalensis* Georgi

6

6.1 Introduction

S. baicalensis Georgi having a common name Baikal skullcap is a member of family Lamiaceae. *S. macrantha* Fisch. is the synonym for *S. baicalensis*. *S. baicalensis* is cultivated in China, Korea, Mongolia, Siberia and the Russian Far East. *S. baicalensis* is one of the 50 fundamental herbs of the *Chinese Materia Medica* and is known as Huang Qin. The root is used in the medicine.

6.2 Botany

S. baicalensis is a perennial plant. The basal part of the stem is prostrate on the ground level and rises up to 15–120 cm. The taproot system is stout and slightly conical. Leaves are opposite, with a short handle, lanceolate blade and entire margin. Racemes are terminal. Labiate flowers are dark brown in colour. Nutlets are four in number, black in colour and almost round.

6.3 Phytochemistry

6.3.1 Flavonoids (Huang et al. 2003; Liu et al. 2011)

Baicalin (baicalein-7-glucuronide) and its aglycone baicalein (5,6,7-trihydroxyflavone) and glycoside, baicalein-7-O-glucoside (oroxin A) (Figs. 6.1, 6.2 and 6.3)

Wogonoside (wogonin-7-glucuronide) and its aglycone wogonin and norwogonin and glycoside, wogonin-5-O-glucoside (Figs. 6.4, 6.5 and 6.6)

Scutellarin and isoscutellarein (Figs. 6.7, 6.8 and 6.9)

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_6

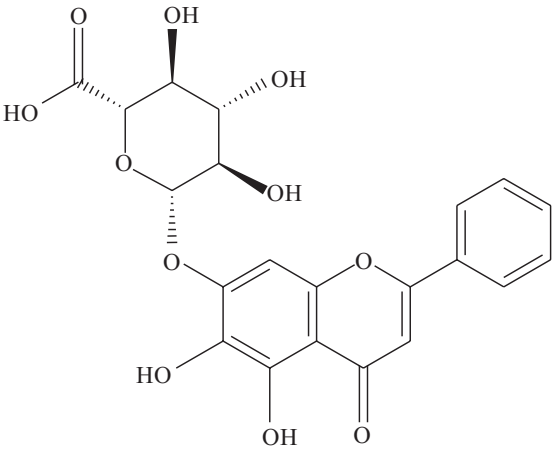


Fig. 6.1 Chemical structure of baicalin

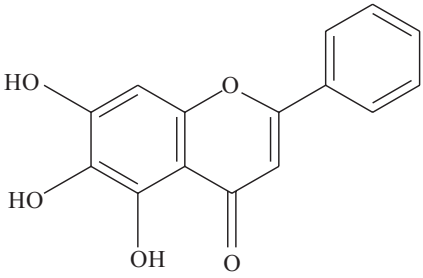


Fig. 6.2 Chemical structure of baicalein

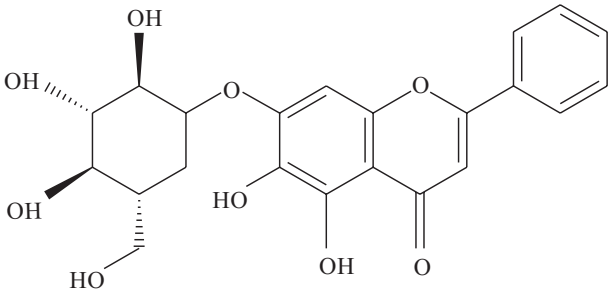


Fig. 6.3 Chemical structure of baicalein-7-O-glucoside

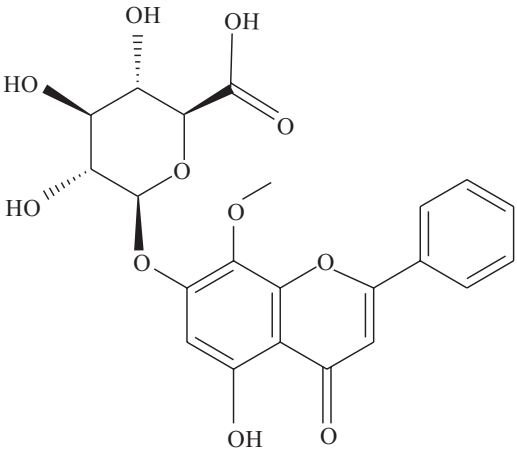


Fig. 6.4 Chemical structure of wogonoside (wogonin-7-glucuronide)

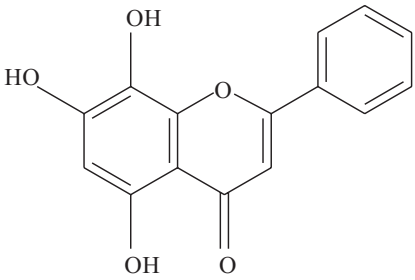


Fig. 6.5 Chemical structure of wogonin

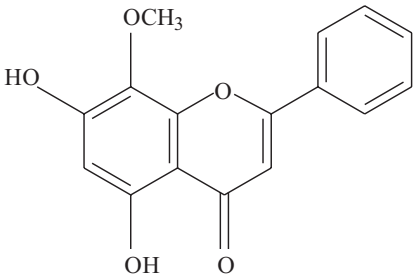


Fig. 6.6 Chemical structure of norwogonin

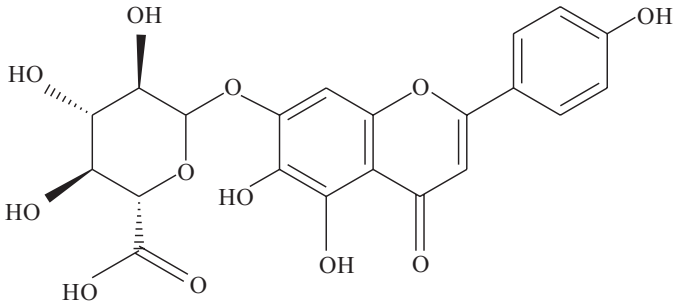


Fig. 6.7 Chemical structure of scutellarin

Fig. 6.8 Chemical structure of isoscutellarein

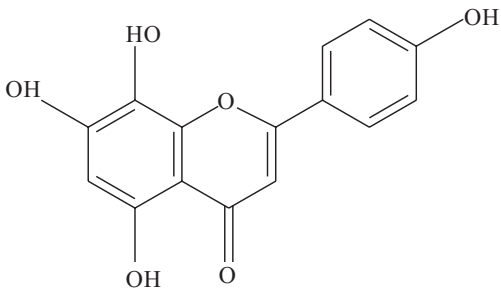
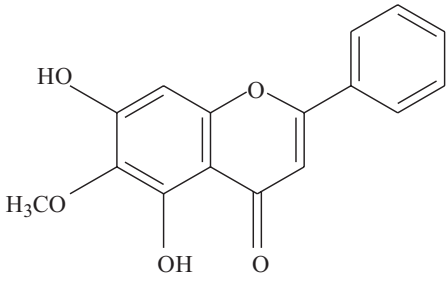


Fig. 6.9 Chemical structure of oroxylin A



6.3.2 Sterol

β-sitosterol

6.3.3 Organic Acids

6.3.4 Flavones (Liao et al. 1998; Martin and Dusek 2002; Wang et al. 2002).

Skullcapflavone I and skullcapflavone II, 6,2′-dihydroxy-5,7,8,6′-tetramethoxyflavone and 5,7,2′-trihydroxy-6,8-dimethoxyflavone (Figs. 6.10, 6.11, 6.12 and 6.13)

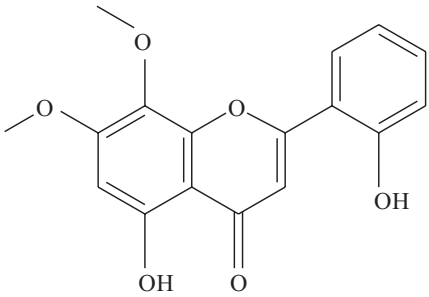


Fig. 6.10 Chemical structure of skullcapflavone I

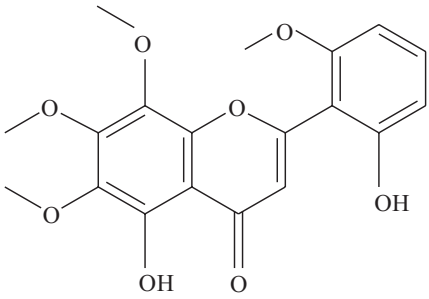


Fig. 6.11 Chemical structure of skullcapflavone II

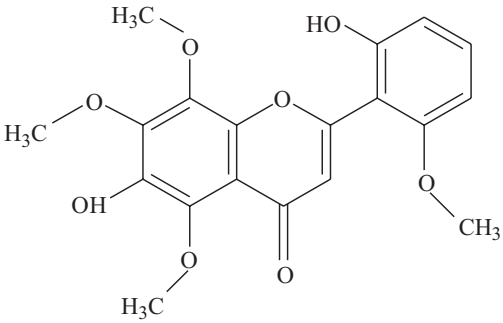


Fig. 6.12 Chemical structure of 6,2′-dihydroxy-5,7,8,6′-tetramethoxyflavone

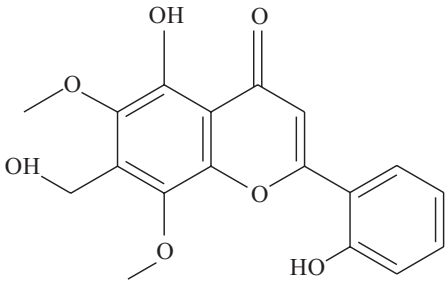


Fig. 6.13 Chemical structure of 5,7,2′-trihydroxy-6,8-dimethoxyflavone

6.4 Actions

Anodyne, antibacterial, antipyretic, antispasmodic, astringent, cholagogue, diuretic, expectorant, febrifuge, haemostatic, hypolipidemic, laxative, mild-sedative, nervine, stomachic and tonic

6.5 Therapeutics

Chronic hepatitis, diarrhoea, dysentery, enteritis, epistaxis, haemoptysis, hypertension, jaundice, malena, threatened abortion and urinary tract infection

6.6 Neuropharmacology

6.6.1 Benzodiazepine Site

Before going into details of the neuropharmacology of *S. baicalensis*, it is important to understand the benzodiazepine site. The GABA receptor (abbreviated as GABAR) is an ionotropic receptor and ligand-gated ion channel. Its endogenous ligand for GABAR is γ-aminobutyric acid (abbreviated as GABA), the chief inhibitory neurotransmitter in the brain. GABAR is the molecular target of the benzodiazepine group of drugs (Fig. 6.14).

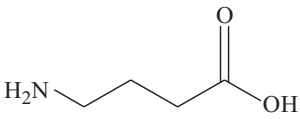


Fig. 6.14 Chemical structure of γ-aminobutyric acid

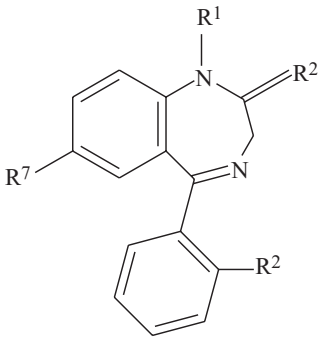


Fig. 6.15 Core structure of benzodiazepines

Benzodiazepines do not bind to the same receptor site on the protein complex as the endogenous ligand GABA (whose binding site is located between α- and β-subunits) but bind to distinct benzodiazepine binding sites situated at the interface between the α- and γ-subunits of α- and γ-subunit containing GABA receptors (Sigel 2000; Akabas 2004) (Fig. 6.15).

The majority of GABA receptors (containing α-, α-, α- or α-subunits) are benzodiazepine sensitive. There exists a minority of GABA receptors (α- or α-subunit containing) which are insensitive to classical 1,4-benzodiazepines (Derry et al. 2004) but instead are sensitive to other classes of GABAergic drugs such as neurosteroids and ethanol.

Peripheral benzodiazepine receptors are known to exist which have no association with GABA receptors. On the recommendation of the International Union of Basic and Clinical Pharmacology (abbreviated as IUPHAR), the terms "BZ receptor," "GABA/BZ receptor" and "omega receptor" are no longer in use and that the term "benzodiazepine receptor" has been replaced with "benzodiazepine site" (Barnard et al. 1988).

6.6.2 Interaction of *S. baicalensis* Flavonoids with the Benzodiazepine Site

The interaction of flavonoids (baicalein and oroxylin A) and flavones (skullcapflavone II) with the benzodiazepine binding site of GABAA receptors was with a Ki value of 13.1, 14.6 and 0.36 micromol/L, respectively (Liao et al. 1998). Based on benzodiazepine site (BZD-S)binding, the order of affinity was wogonin > baicalein > scutellarein > baicalin (Hui et al. 2000).

An experimental study demonstrated affinity of flavones 6,2′-dihydroxy-5,7,8,6′-tetramethoxyflavone and 5,7,2′-trihydroxy-6,8-dimethoxyflavone with benzodiazepine site of the GABAA receptor complex (Wang et al. 2002).

6.6.3 Anticonvulsant Effect of Wogonin

A study investigated the effects of wogonin isolated from *S. baicalensis* on convulsion-related behaviours in mice or rats. Wogonin was intraperitoneally (i.p.) injected into mice or rats 30 min prior to testing. Wogonin significantly blocked convulsion induced by pentylenetetrazole (formerly used as an analeptic) and electroshock induced by strychnine (an alkaloid from the seeds of the *Strychnos nux-vomica*) (Figs. 6.16 and 6.17).

Wogonin caused significant reduction in the electrogenic response score, but flumazenil (a selective benzodiazepine receptor antagonist) caused reversal of this decrease to the level of the control group (Fig. 6.18).

The treatment with wogonin increased the chloride (−) influx into the intracellular area with increasing dose. The treatment with flumazenil and bicuculline caused inhibition of the chloride (−) influx induced by wogonin (Park et al. 2007) (Fig. 6.19).

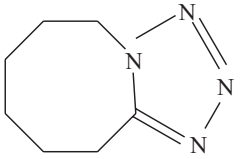


Fig. 6.16 Structure of pentylenetetrazole

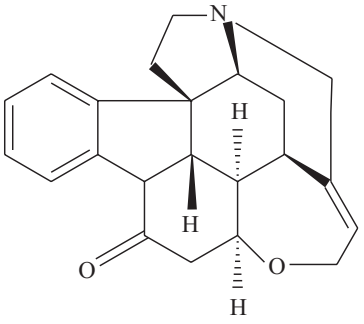


Fig. 6.17 Structure of strychnine

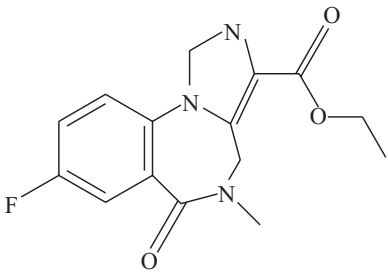


Fig. 6.18 Structure of flumazenil

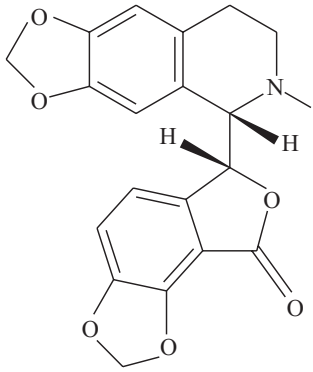


Fig. 6.19 Structure of bicuculline

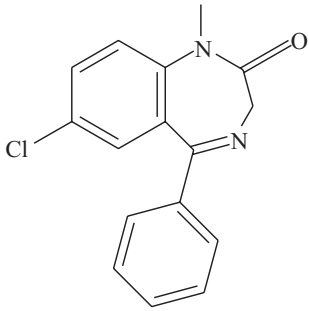


Fig. 6.20 Structure of diazepam

6.6.4 Anxiolytic Effect of Wogonin

Wogonin administered by oral route in a dose of 7.5–30 mg/kg demonstrated a significant anxiolytic activity similar to diazepam in the elevated plus-maze. Co-administration of Ro15-1788(flumazenil) blocked the anxiolytic activity. In the holeboard test, mice treated with wogonin experienced an increased number of head-dips. They spent more time at it, without any sedation (Fig. 6.20).

6.6.5 Neuroprotective Effect of Baicalein

Rats were pretreated with baicalein for 7 days followed by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine for 4 consecutive days. Baicalein improved the abnormal behaviour in MPTP-treated mice (Cheng et al. 2008) (Fig. 6.21).

The results of an in vivo study showed that baicalein exert anti-inflammatory activity by inhibition of α-synuclein aggregation, inflammasome activation and cathepsin B production in the 1-methyl-4-phenylpyridinium ($MPP^{+)}$-infused substantia nigra. The therapeutic importance of baicalein is due to inhibition of MPP^{+}-induced apoptosis. Autophagy in the nigrostriatal dopaminergic system of rat brain also contributes to therapeutic importance of the compound (Hung et al. 2016) (Fig. 6.22).

6.6.6 Anti-amnesic Study of Oroxylin A

Oroxylin A in a dose of 5 mg/kg caused significant reversal of cognitive impairment in animals by passive avoidance and the Y-maze testing. The compound caused an improvement of escape latencies in training trial. It further increased the swimming time and distance within the target zone of the Morris water maze. The ameliorating effect of the compound was antagonized by diazepam and muscimol (Kim et al. 2007).

Abeta(25–35) peptide was administered by intracerebroventricular injection in a dose of 5 nmol. In the acute study, oroxylin A in dose of 5 mg/kg p.o. significantly reversed the Abeta(25–35) peptide-induced cognitive impairments as suggested by passive avoidance and Y-maze task findings. In the subchronic study, treatment with oroxylin A in dose of 5 mg/kg, p.o. for 1 week caused amelioration of cognitive impairments induced by Abeta(25–35) peptide (Kim et al. 2008).

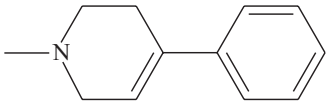


Fig. 6.21 Chemical structure of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

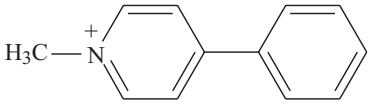


Fig. 6.22 Chemical structure of 1-methyl-4-phenylpyridinium

6.7 *Scutellaria barbata* D.Don

Common Name Barbat skullcap

Distribution Native to Asia

Botany *S. barbata* is a perennial herb growing up to 35 cm tall. The leaves are lance shaped or triangular. The flowers are purple-blue in colour and bone on pedicels having sharp bracteoles.

Chemistry Flavonoids and diterpenoids (Wu et al. 2015)

6.7.1 Preclinical Neuropharmacology

6.7.1.1 Alzheimer's Disease

The flavonoids has been reported to alleviate memory deficits and neuronal injuries induced by composited Aβ in rats (Wu et al. 2016).

6.8 *Scutellaria lateriflora* L.

Common Name American skullcap, blue skullcap, mad dog skullcap and side-flowering skullcap

Distribution Native to North America

Botany *S. lateriflora* is an upright plant growing 60 to 80 cm. The blue flowers are just under a cm long.

Chemistry Flavonoids: baicalin and baicalein and dihydropyranocoumarins (Li et al. 2009)

(Awad et al. 2003)

Action Sedative

Therapeutics *S. lateriflora* is used to treat anxiety neurosis (Awad et al. 2003).

6.8.1 Preclinical Neuropharmacology

6.8.1.1 Anticonvulsant

S. lateriflora was studied for anticonvulsant activity in a rat model of acute seizure induced by pilocarpine and pentylenetetrazol. *S. lateriflora* showed significant anticonvulsant activity (Zhang et al. 2009).

6.8.2 Clinical Neuropharmacology

A. A double-blind, placebo-controlled study involving healthy volunteers showed significant anxiolytic effect of American skullcap (Wolfson and Hoffmann 2003).
B. A randomized, double-blind placebo-controlled crossover study in healthy volunteers reported significant mood-enhancing activity without decrease in cognition (Brock et al. 2014).

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Piper methysticum G.Forst: A Potent Antianxiety Agent

7

Taxonomical Nomenclature

Kingdom:	Plantae
Unranked:	Angiosperms
Unranked:	Magnoliids
Order:	Piperales
Family:	Piperaceae
Genus:	*Piper*
Species:	*methysticum*

7.1 Introduction

P. methysticum is native to Pacific Island region. It is popularly known as kava-kava. The name kava stands for the beverage prepared from *P. methysticum.* The beverage is used for drinking purpose in ceremonies (Garner and Klinger 1985). The variants of the name include awa and kawa (Lebot et al. 1992; Dentali 1997).

The Pacific cultures of Polynesia including Hawaii, Melanesia, Micronesia (few parts) and Vanuatu utilize Kava for sedative action (Readon 1960; Riesenberg 1967; Balick and Roberta 2000). Kava is an important ingredient in modern Samoan culture, Cook Islands and Tonga (Holmes 1967; Lemert 1967, 1976).

7.2 Botany

P. methysticum is a branched, erect shrub growing 12 feet high. The roots are thick in fresh form but harden in dried form. The stem is succulent and thick and has many colours. The plant produces small, sterile flower spike yellow-green in colour (Wagner et al. 1990).

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_7

7.3 Chemistry (Klohs et al. 1959; Shulgin 1973)

7.3.1 Kavalactones (or Kavapyrones)

Kavalactones (Fig. 7.1) are group of lactone compounds. Kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin and desmethoxyyangonin are the main kavalactones (Figs. 7.1, 7.2, 7.3, 7.4, 7.5, 7.6 and 7.7).

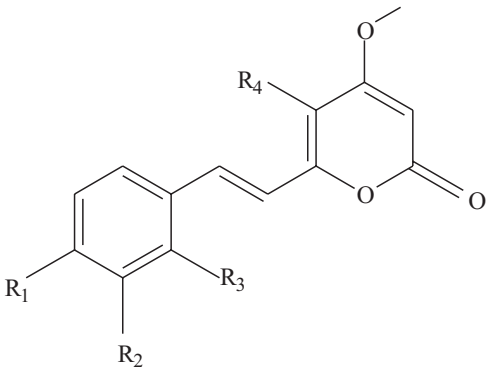

Fig. 7.1 The general structure of kavalactones

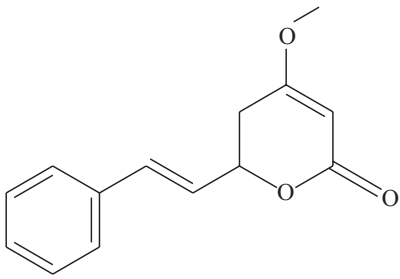

Fig. 7.2 The structure of kavain

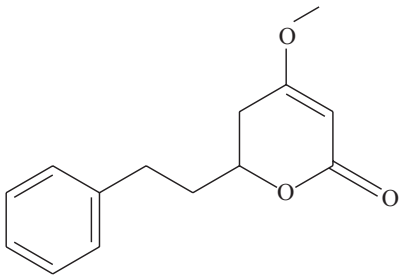

Fig. 7.3 The structure of dihydrokavain

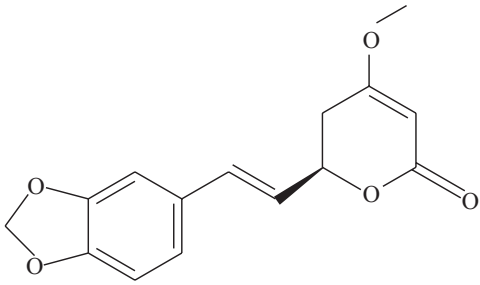

Fig. 7.4 The structure of methysticin

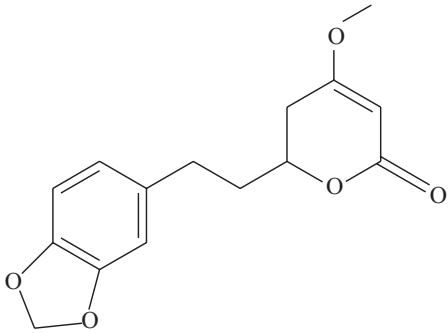

Fig. 7.5 The structure of dihydromethysticin

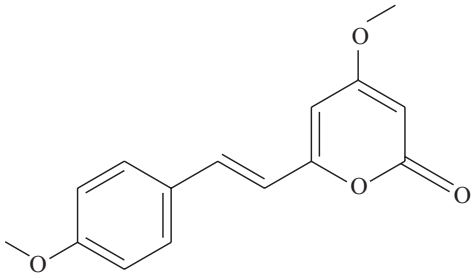

Fig. 7.6 The structure of yangonin

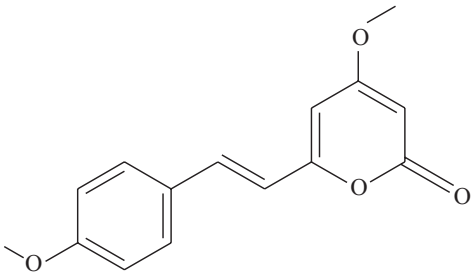

Fig. 7.7 The structure of desmethoxyyangonin

7.3.2 Piperidine Alkaloids

Pipermethystine is present in the aerial parts. It is toxic in nature. Kava root preparations prepared in a correct way are devoid of this alkaloid. However, false-positive alkaloid reactions were obtained with extracts of *P. methysticum* (Furgiele et al. 1962). 3alpha, 4alpha-epoxy-5beta-pipermethystine and awaine have been reported (Dragull et al. 2003) (Fig. 7.8).

7.3.3 Chalcones: Flavokavain A–C (Figs. 7.9, 7.10, 7.11 and 7.12)

7.4 Traditional Medicinal Use

In traditional medicine, the plant is used in the treatment of anxiety neurosis.

7.5 Neuropharmacology of Kava-Kava

7.5.1 Antianxiety or Anxiolytic

Kava-kava has been described as an herbal sedative and an alternative anxiolytic (Kinder and Cupp 1998; Nowakowska et al. 1998; Pittler and Ernst 2002). There has been growing evidence about the efficacy and safety of kava-kava in the treatment of anxiety and stress (Müller and Komorek 1999; Bilia et al. 2002). The therapeutic potential of kava-kava in the treatment of anxiety disorders and safety has been elaborated (Saeed et al. 2008; Singh and Singh 2002).

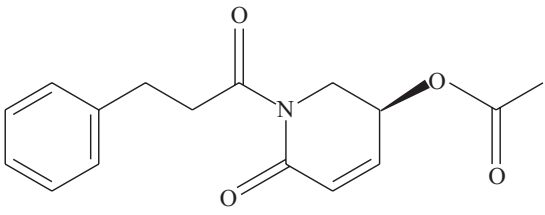

Fig. 7.8 The structure of pipermethystine

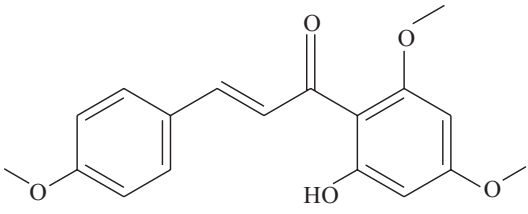

Fig. 7.9 The structure of flavokavain A

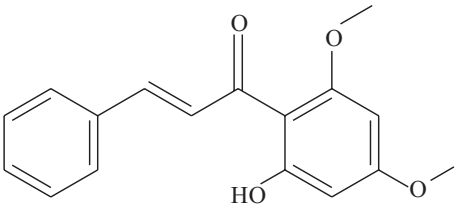

Fig. 7.10 The structure of flavokavain B

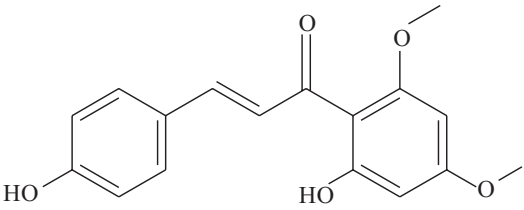

Fig. 7.11 The structure of flavokavain C

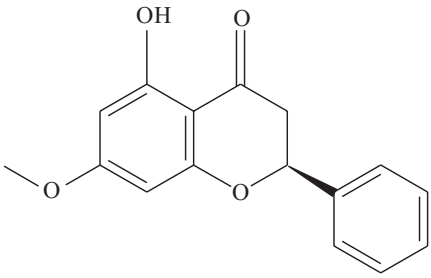

Fig. 7.12 The structure of pinostrobin

A double-blind study with placebos lasting for 28 days reported favourable effect of a special extract of kava-kava in patients suffering from anxiety, tension and excitation states of nonpsychotic genesis (Kinzler et al. 1991).

A double-blind placebo-controlled study lasting for 28 days reported the efficacy of special extract of kava-kava in patients with states of anxiety, tension and excitedness of nonmental origin (Lehmann et al. 1996).

A randomized placebo-controlled outpatient trial lasting for 25 weeks reported efficacy of *P. methysticum* extract in the treatment of anxiety (Volz and Kieser 1997). An observational study on outpatients reported efficacy of *P. methysticum* extract in the treatment of anxiety disorders (Scherer 1998). Successful treatment of stress-induced insomnia with the extract singly and in combination with *Valeriana officinalis* (Wheatly 2001).

Combination of *P. methysticum* extract and hormone replacement therapy (HRT) in treating postmenopause anxiety has shown encouraging results (De Leo et al. 2000). The administration of kava-kava in perimenopausal women has been shown to reduce the incidence of anxiety (Cagnacci et al. 2003). An 8-week randomized, double-blind multicentre clinical trial involving 129 outpatients diagnosed with generalized anxiety disorder (GAD) reported efficacy of kava-kava extract as

effective as opipramol and buspirone in generalized anxiety disorder (Boerner et al. 2003) (Figs. 7.13 and 7.14).

In the chick social separation-stress paradigm, anxiolytic (antianxiety) effects of kava-kava extract and kavalactones and fractions have been reported (Smith et al. 2001; Feltenstein et al. 2003).

In a study, kava extract resulted in a significant, dose-dependent anxiolytic effect in rat model of anxiety. The effect was not mediated through the benzodiazepine binding site on the GABAA receptor complex (Garret et al. 2003).

A multicentre, randomized, placebo-controlled, double-blind clinical trial reported clinical efficacy of *P. methysticum* extract in insomnia associated with anxiety disorders (Lehrl 2004).

A placebo-controlled double-blind outpatient trial reported efficacy of *P. methysticum* extract in patients diagnosed with nonpsychotic anxiety (Geier and Konstantinowicz 2004).

A study evaluated the efficacy and safety of *P. methysticum* in the treatment of generalized anxiety disorder. Analysis of the data was done from three randomized, double-blind, placebo-controlled trials of *P. methysticum*, including one study with venlafaxine, in adult outpatients with DSM-IV generalized anxiety disorder. Findings of the three controlled trials do not support the use of *P. methysticum* in DSM-IV generalized anxiety disorder (Connor et al. 2006) (Fig. 7.15).

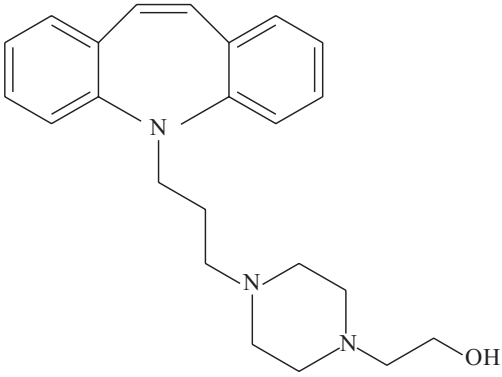

Fig. 7.13 The structure of opipramol – a tricyclic antidepressant

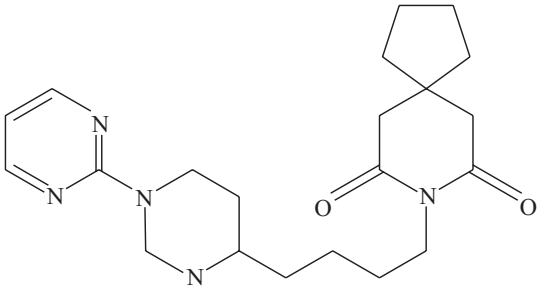

Fig. 7.14 The structure of buspirone – an azaspirodecanedione class of antidepressant

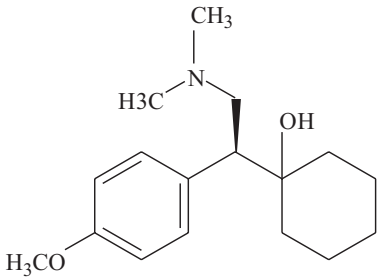

Fig. 7.15 The structure of venlafaxine – the serotonin-norepinephrine reuptake inhibitor

A randomized, placebo-controlled crossover trial popularly known as the Kava Anxiety Depression Spectrum Study using an aqueous extract of *P. methysticum* demonstrated potential anxiolytic (antianxiety) and antidepressant activity. The dose used in the study was found to be safe (Sarris et al. 2009).

A double-blind, randomized, placebo-controlled study reported moderate effect of *P. methysticum* as a short-term treatment of generalized anxiety disorder (GAD) (Sarris et al. 2013).

In vitro effects of *P. methysticum* extract and pure synthetic kava pyrones on human platelet MAO-B was investigated in comparison to amitriptyline, imipramine and brofaromine. Kava-kava extract reversibly inhibited MAO-B in intact platelets (IC50 24 microM). The order of potency was desmethoxyyangonin > (+/−)-methysticin > yangonin > (+/−)-dihydromethysticin > (+/−)- dihydrokavain > (+/−)-kavain (Uebelhack et al. 1998) (Figs. 7.16, 7.17 and 7.18).

7.5.2 Anticonvulsant

Kavapyrones (dihydromethysticin and dihydrokavain) have been reported to inhibit electroconvulsions and chemical-induced convulsions (Meyer and Meyer-Burg 1964; Meyer 1964).

A study investigated the anticonvulsant effect of kava-kava alone or in combination with a diazepam. The results were suggestive of the possibility of combining a low-dose diazepam with kava-kava so as to reduce the incidence of side effects and for clinical usage in patients on chronic treatment with diazepam (Tawfiq et al. 2014).

7.5.2.1 Drug Interactions

Alprazolam

A case reported coma from the health food store probably due to interaction between kava and alprazolam (Almeida and Grimsley 1996) (Fig. 7.19).

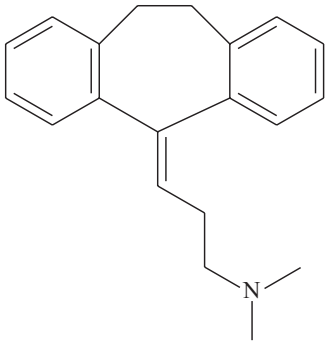

Fig. 7.16 The structure of amitriptyline – a tricyclic antidepressant

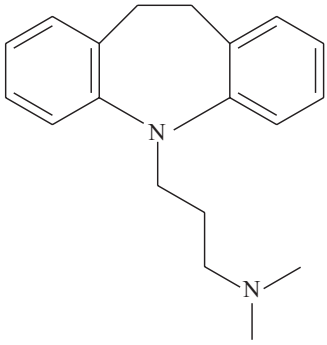

Fig. 7.17 The structure of imipramine – a tricyclic antidepressant

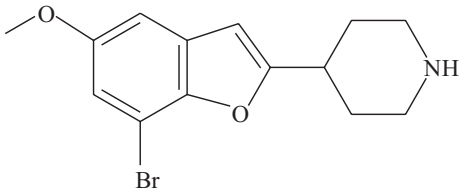

Fig. 7.18 The structure of brofaromine – a reversible inhibitor of monoamine oxidase A

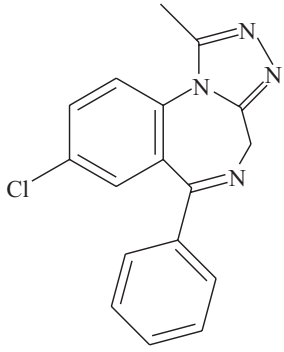

Fig. 7.19 The structure of alprazolam – a short-acting benzodiazepine anxiolytic

7.6 Neuropharmacology of Kavain

7.6.1 Preclinical Pharmacology

Kavain is considered to be active principle of kava-kava extracts (Schliack 1967; Kretschmer 1970, 1974). Kavain is weakly Na + antagonistic and therefore antiepileptic. Kavain has pronounced L- type Ca2+ channel antagonistic properties and acts as a positive modulator of the early K+ outward current, a factor contributing to mood stabilizing properties similar to lamotrigine (Grunze et al. 2001) (Fig. 7.20).

A study was undertaken to investigate the protective effects of (+/−)-kavain in the experimental 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. (+/−)-kavain failed to influence the metabolism of MPTP. The antiglutamatergic effect of (+/−)-kavain was considered to be responsible for neuroprotective effects against MPTP toxicity (Schmidt and Ferger 2001).

Kavain and rilmazafone (a benzodiazepine prodrug) showed a significant shortening in sleep latency, decreased awake time and increased non-rapid eye movement sleep time. Following the administration of diphenhydramine, significant shortening of the sleep latency was observed (Tsutsui et al. 2009).

7.6.2 Clinical Pharmacology

In a placebo-controlled double-blind clinical study, D,L-kavain or oxazepam proved to be equivalent as far as the nature and potency of anxiolytic action was concerned. No adverse drug reaction was noticed (Lindenberg and Pitule-Schödel 1990) (Figs. 7.21 and 7.22).

Kavain has been shown to potentiate GABAA receptors. The modulating effect of kavain remained was not affected by flumazenil, providing evidence that kavain did not enhance the GABAA receptor via the benzodiazepine binding site (Chua et al. 2016).

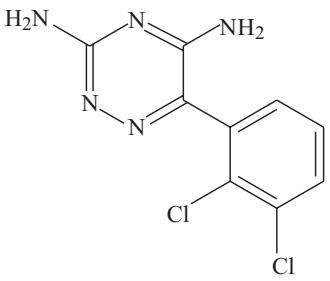

Fig. 7.20 The structure of lamotrigine – an anticonvulsant agent

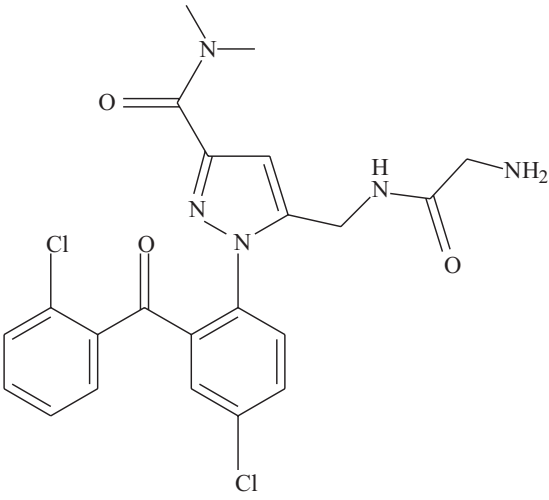

Fig. 7.21 The structure of rilmazafone – a hypnotic and sedative benzodiazepine

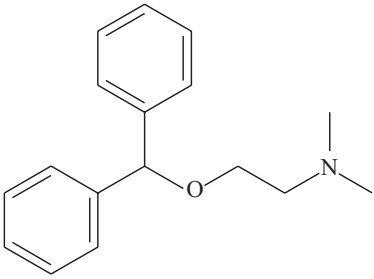

Fig. 7.22 The structure of diphenhydramine – an antihistaminic

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Neuropharmacology of *Melissa officinalis* L.

8

8.1 Introduction

Melissa officinalis L. (Lamiaceae), commonly known as lemon balm, is an important plant of herbal materia medica. The plant is native to Central Asia and South-Central Europe. Now, *M. officinalis* is widely naturalized in the United States and the rest of the world.

As already discussed in Chap. 2, the plant is reputed as sedative from the Middle Ages (Glowatzki 1970). Paracelsus, the founder of toxicology, was well aware about the properties of *M. officinalis* (Kerner 1965). The plant finds wide use in alternative medicine and aromatherapy. The leaves are used in medicine. Tea, essential oil, tincture and extract are prepared from the leaves. The tea is used to promote sleep and cognition (Morelli 1977).

8.2 Botany

M. officinalis grows up to 2 ft. high. The leaves are deeply wrinkled and the colours vary from yellowish green to dark green. Clusters of small flowers, light yellow in colour, appear in the spring and summer season. The flowers originate at the meeting point of the leaves and stem.

8.3 Chemistry

M. officinalis contains essential oil, flavonoids, polyphenolics (melitric acids A and B and rosmarinic acid), triterpenes and phenylpropanoid heteroside: eugenylglucoside (Hefendehl 1970; Thieme and Kitze 1973; Brieskorn and Krause 1974; Morelli 1977; Tittel et al. 1982; Mulkens and Kapetanidis 1988; Agata et al. 1993; Hanganu et al. 2008) (Figs. 8.1, 8.2 and 8.3).

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_8

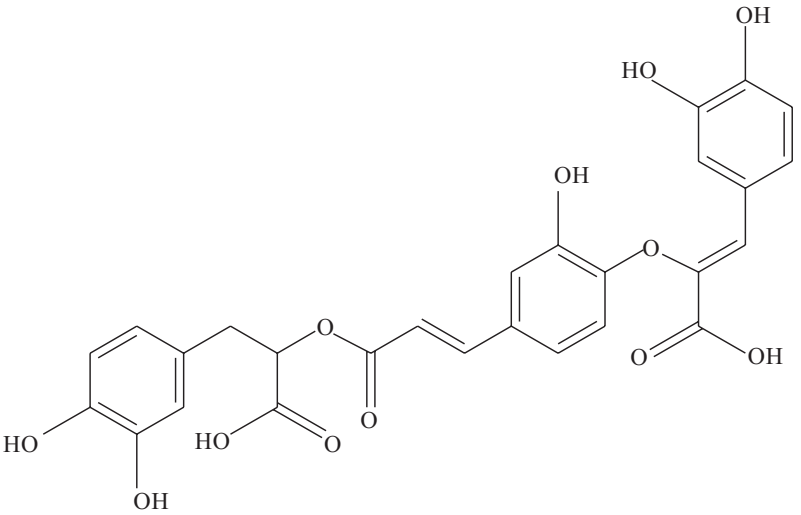

Fig. 8.1 Structure of melitric acid A

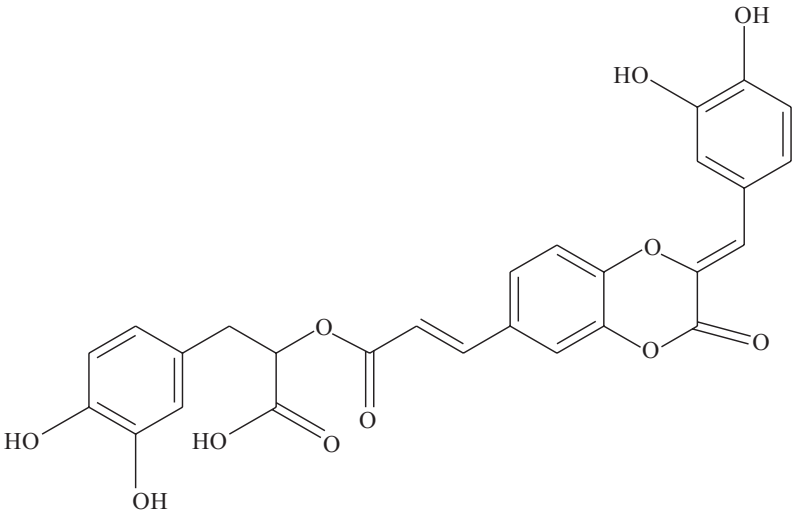

Fig. 8.2 Structure of melitric acid B

8.4 Preclinical Neuropharmacology

8.4.1 Antianxiety and Antidepressant

In vitro rat brain homogenate assays were utilized for determination of the inhibitory concentrations of water and ethanolic extracts of *Centella asiatica*, *Humulus lupulus*, *Matricaria recutita*, *Melissa officinalis* and *Valeriana officinalis*. The water

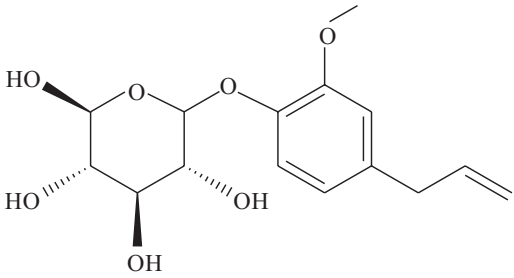

Fig. 8.3 Structure of eugenylglucoside

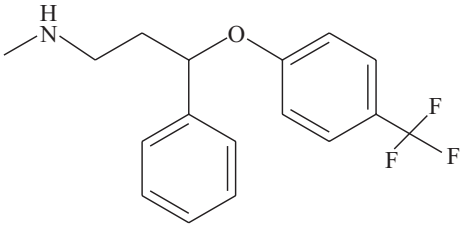

Fig. 8.4 Structure of fluoxetine

extract of *M. officinalis* showed the largest inhibition of ϒ-aminobutyric acid transaminase activity with IC50 value worth 0.35 mg/mL (Awad et al. 2007).

In elevated plus-maze test (one of the commonly used tests for research in anxiety), the percentage of open entries and open-arm times of males and females given with subacute dose of the ethanolic extract of *M. officinalis* were significantly higher than those of the vehicle-treated animals. The levels were however similar to those seen in the group on diazepam.

In the forced swimming test (this is used to research depression-like behaviour in animals), the duration of immobility was found to be significantly lower in males and females treated with the ethanolic extract of *M. officinalis* as compared to vehicle-treated counterparts. However, the antidepressant response produced by a 10-day treatment with fluoxetine was more effective as compared to *M. officinalis* extract (Taiwo et al. 2012) (Fig. 8.4).

In the forced swimming test, water extract of *M. officinalis* and rosmarinic acid (active ingredient in the extract) resulted in significant reduction in depression-like illness. The study demonstrated the serotonergic antidepressant-like activity of water extract of *M. officinalis* (Lin et al. 2015).

8.5 Clinical Neuropharmacology

8.5.1 Anxiolytic

A. In a double-blind, placebo-controlled, randomized experimental study, 18 healthy volunteers were administered a standardized extract of *M. officinalis* in doses of 300 and 600 mg on separate days separated by a 7-day washout period.

The result of the study showed that the dose of 600 mg caused significant increase in self-ratings of calmness and reduced self-ratings of alertness (Kennedy et al. 2004).

B. In yet another double-blind, placebo-controlled, randomized, balanced crossover trial, 24 healthy volunteers were administered a standardized product containing *M. officinalis* and *V. officinalis* in doses of 600, 1200 and 1800 mg on separate days separated by a 7-day washout period. The result of the study showed that the dose combination was having potential anxiolytic activity requiring further investigation (Kennedy et al. 2006).
C. A pilot trial reported efficacy of the leaf extract of *M. officinalis* in treating of volunteers diagnosed with mild-to-moderate anxiety neurosis associated with sleep disturbance (Cases et al. 2011).

8.5.2 Cognition

A. Modulation of cognitive and mood performance was observed in 20 healthy participants following acute administration of *M. officinalis* in a randomized, placebo-controlled, double-blind, balanced crossover study (Kennedy et al. 2002).
B. Modulation of cognitive and mood performance was observed in 20 healthy participants following administration of encapsulated dried leaf of *M. officinalis* in doses of 600, 1000 and 1600 mg in a randomized, placebo-controlled, double-blind, balanced crossover study (Kennedy et al. 2003).

8.5.3 Dementia

A. Treatment with essential oil of *M. officinalis* in 21 patients suffering from severe dementia was found to be effective and safe. Sixty percent of the active treatment group and fourteen percent of the placebo-treated group reported a thirty percent reduction of Cohen-Mansfield Agitation Inventory score. An overall improvement in the incidence of agitation of 35% in patients taking essential oil of *M. officinalis* was observed and 11% in those treated with placebo (Ballard et al. 2002).
B. A double-blind placebo-controlled randomized trial involving 114 participants investigated the utility of essential oil of *M. officinalis* and donepezil (used to improve cognition and behaviour of people with Alzheimer's) for treating agitation in people suffering from Alzheimer's disease. The Pittsburgh Agitation Scale, Neuropsychiatric Inventory and other outcome measures were completed at baseline, 4-week and 12-week follow-ups. The results showed no evidence that essential oil of *M. officinalis* was superior to donepezil or placebo in treating agitation in people diagnosed with Alzheimer's disease (Burns et al. 2011) (Fig. 8.5).

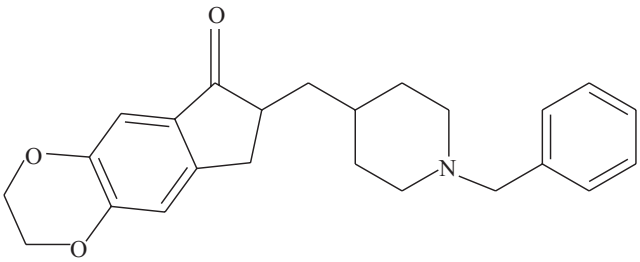

Fig. 8.5 Structure of donepezil

8.5.3.1 Restlessness and Dyssomnia

An open, multicentre study in children age group of less than 12 years suffering from restlessness and nervous dyskoimesis reported utility of combination of *M. officinalis* and *V. officinalis* (Muller and Klement 2006).

8.5.3.2 Sleep Disorders

A clinical study in 100 women aged 50–60 years explored the utility of a combination of *M. officinalis* and *V. Officinalis* in sleep disorders during the menopause. The Pittsburgh Sleep Quality Index was used as pre- and post-intervention. A striking difference was the reduction in the incidence of sleep disorders in the experimental group as compared to the placebo (Taavoni et al. 2013).

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Neuropharmacology of Chamomiles

9

9.1 *Matricaria recutita* L. (Asteraceae)

The synonym is *M. chamomilla* L., and *M. recutita* is commonly known as German chamomile and true chamomile (Kreitmair 1951). The plant is native to Afghanistan, Europe and Iran (Formentini and Rocchi 1961). The dried flower heads are utilized in ethnomedicine for preparation of tea with antispasmodic (spasmolytic) and sedative properties (Viola et al. 1995).

9.1.1 Botany

M. recutita grows to a height of 15–60 cm. The stem is smooth, branched and erect. The leaves are bipinnate or tripinnate. The flowers are borne in heads called capitula.

9.1.2 Chemistry

Essential oil contains chamazulene and α-bisabolol (Luppold 1984). In addition, it contains flavones and coumarins.

9.1.3 Preclinical Neuropharmacology

9.1.3.1 Stimulant-Like Effect

The essential oil of *M. recutita* at doses of 50 and 100 mg/kg resulted in significant increase in the numbers of spontaneous locomotor activities. In the elevated plus-maze, open field and social interaction tests, the essential oil exhibited anxiogenic activity. The essential oil decreased the mobility of the animals in tail suspension tests (Can et al. 2012).

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_9

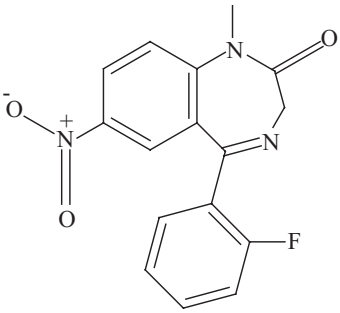

Fig. 9.1 Structure of flunitrazepam – an intermediate-acting benzodiazepine

9.1.3.2 Anxiolytic

Apigenin, a flavonoid obtained from fractionation of the aqueous extract of *M. recutita*, resulted in competitive inhibition of the binding of flunitrazepam (an intermediate-acting benzodiazepine) with a Ki of 4 microM. The flavonoid showed a significant anxiolytic activity in the elevated plus-maze test in mice (Viola et al. 1995) (Fig. 9.1).

9.1.3.3 Neuroprotective

The methanolic extract of *M. recutita* demonstrated neuroprotective activity in a dose-dependent manner. The methanolic extract significantly reduced the cerebral infarction area in comparison with ischemia/reperfusion group (Chandrashekhar et al. 2010).

The methanolic extract of *M. recutita* demonstrated neuroprotective activity against aluminium fluoride-induced oxidative stress in rats. The neuroprotective activity was evident from the increase in enzymes (superoxide dismutase, catalase), glutathione and total thiol levels and decrease in lipid peroxidation as compared to negative control group (Ranpariya et al. 2011).

9.1.4 Clinical Neuropharmacology

9.1.4.1 Antidepressant

An exploratory study reported efficacy of *M. chamomilla* in the treatment of depression. *M. chamomilla* significantly reduced over time in Hamilton Depression Rating scores as compared to placebo in all participants (Amsterdam et al. 2012).

9.1.4.2 Generalized Anxiety Disorder

Three clinical studies reported efficacy of *M. chamomilla* in the treatment of generalized anxiety disorder (GAD) (Amsterdam et al. 2009; Mao et al. 2016; Keefe et al. 2016).

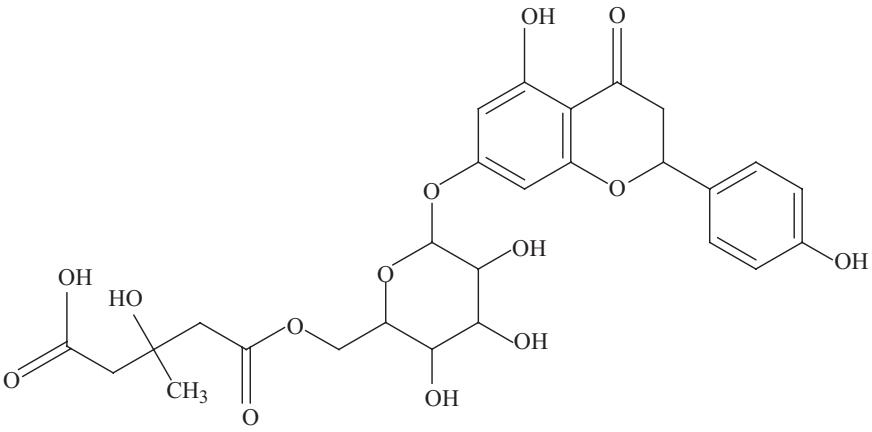

Fig. 9.2 Structure of chamaemeloside

9.2 *Chamaemelum nobile* (L.) All. (Asteraceae)

The synonym is *Anthemis nobilis* L. The plant is popularly known as Roman chamomile, English chamomile and low chamomile which are relatively less popular names. *C. nobile* is native to Western Europe.

9.2.1 Botany

C. nobile is an evergreen perennial plant. The stem is procumbent. The leaves are alternate, bipinnate, finely dissected and downy to glabrous. The flowers are daisy-like and white in colour (Mabey 1996; Grigson 1996).

9.2.2 Chemistry

Essential oil contains coumarins and flavonoids. Chamaemeloside is the major polyphenolic compound in the tea (Carnat et al. 2004) (Fig. 9.2).

9.2.3 Traditional Medicinal Use

The plant is used for the same applications as *M. recutita*.

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Neuropharmacology of *Bacopa monnieri* with Reference to Bacosides

10

Classification

Kingdom:	Plantae
Division:	Angiospermae
Class:	Dicotyledonae
Subclass:	Gamopetalae
Series:	Bicarpellatae
Order:	Personale
Family:	Scrophulariaceae
Genus :	*Bacopa*
Species :	*monnieri*

10.1 Introduction

Bacopa monnieri L. is commonly known as thyme-leaved *Gratiola* or water hyssop. In Ayurveda, the plant has been described as a brain tonic. The plant is widely distributed throughout warmer parts of the world.

10.2 Botany

B. monniera is a small, creeping, succulent herb. The leaf- and flower-bearing stems arise from creeping stems that form roots at the nodes. The leaves are simple, with entire margins. Flowers are blue or white with purple veins, and fruit is capsule with numerous seeds.

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_10

10.3 Chemistry

Triterpenoid Saponins Bacosides include bacosides A, A_1, A_3 and B (Chatterji et al. 1965; Basu et al. 1967; Jain and Kulshreshtha 1993; Rastogi et al. 1994), and bacopasides include bacopasides I–XI (Chakravarty et al. 2001; Hou et al. 2002; Chakravarty et al. 2003). Bacosides A and B are optical isomers (Deepak and Amit 2004; Deepak and Amit 2013).

Dammarane-Type Saponins They are known as bacopasaponins (Garai et al. 1996a, b).

The bacoside A content is about 2.5–3.0%. Bacoside A on acid hydrolysis gives an aglycone (nonsugar) fraction and a mixture of three sugars. Bacoside A has been shown to be a mixture of bacoside A3, bacopaside II, bacopaside X and bacopasaponin C (Deepak et al. 2005).

Bacoside B is obtained as colourless needles from methanolic extract. It is sparingly soluble in ethanol, methanol and water. On acid hydrolysis, bacosides A and B yield aglycones called bacogenins A_1, A_2, A_3 and A_4. The standardization of Brahmi vati has been done on the basis of bacoside A, bacoside A3 and piperine (Mishra et al. 2013a, b) (Figs. 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8 and 10.9).

Cucurbitacins Bacobitacin A–D and cucurbitacin E (Bhandari et al. 2007) (Fig. 10.10)

Alkaloids Herpestine and brahmine

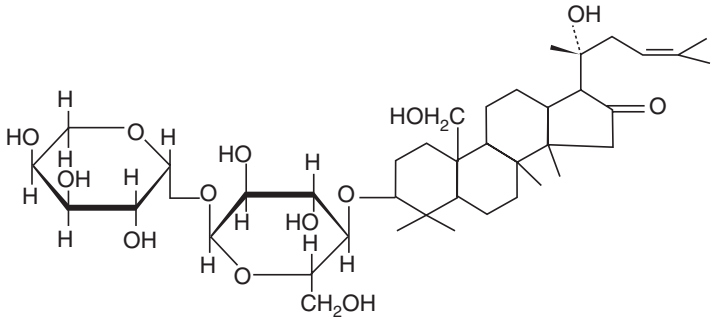


Fig. 10.1 Structure of bacoside A

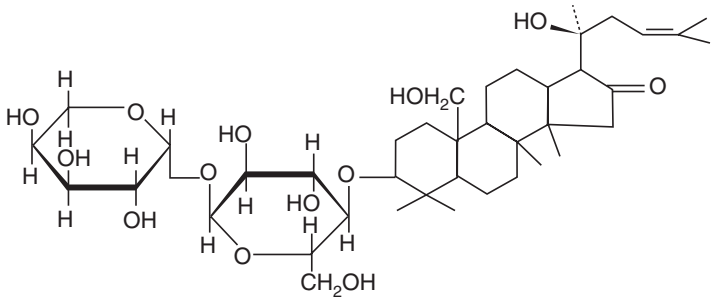


Fig. 10.2 Structure of bacoside B

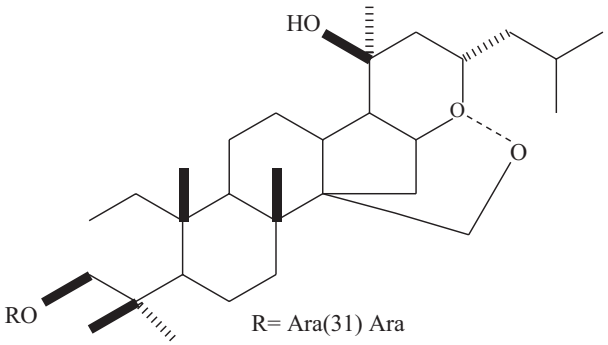


Fig. 10.3 Structure of bacoside A_1

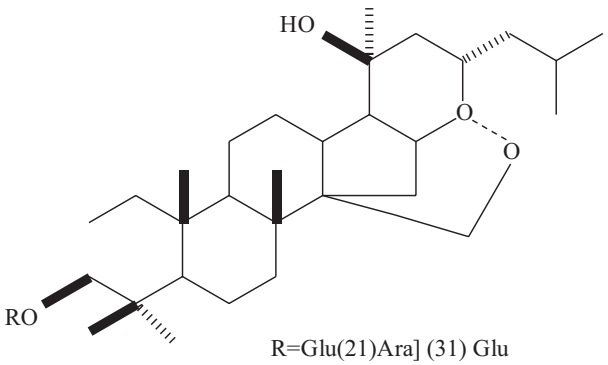
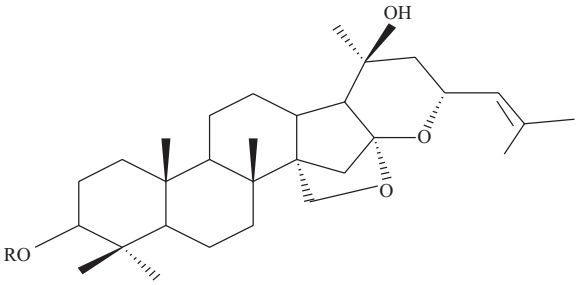
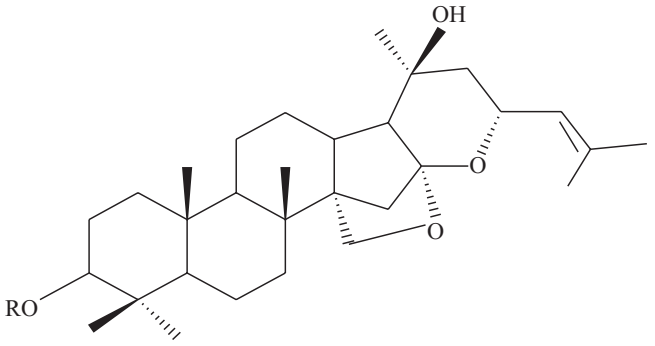


Fig. 10.4 Structure of bacoside A_3



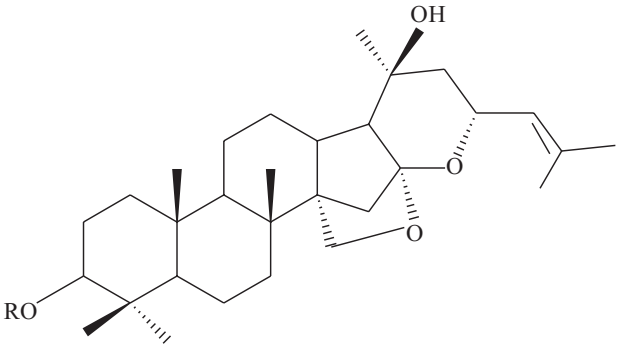
Alpha-L-arabinofuranosyl (1⟶2)-[6-O-sulphonyl-Beta-D-glucopyranosyl-(1⟶3)]-Alpha-L-arabinopyranosyl

Fig. 10.5 Structure of bacopaside I



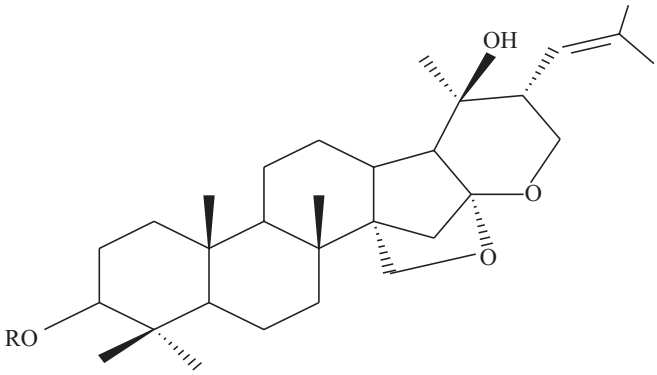
Alpha-L-arabinofuranosyl (1⟶2)-[Beta-D-glucopyranosyl-(1⟶3)]-Beta-D-glucopyranosyl

Fig. 10.6 Structure of bacopaside II



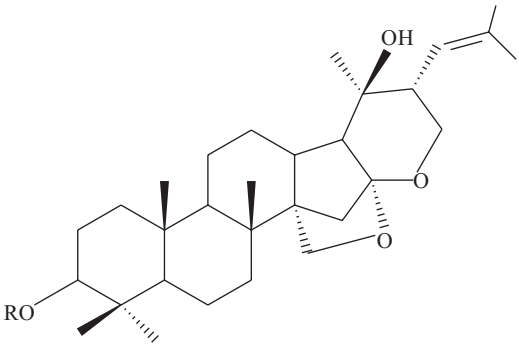
Beta-D-glucopyranosyl-(1⟶3)-Alpha-L-arabinpyranosyl

Fig. 10.7 Structure of bacopaside IV



Beta-D-glucopyranosyl-(1→3)-Alpha-L-arabinopyranosyl

Fig. 10.8 Structure of bacopaside V



R=Alpha-L-arabinofuranosyl(1→2)-[Beta-D-glucopyranosyl1-(1→3)]-Alpha-L-arabinopyranosyl

Fig. 10.9 Structure of bacopasaponin C

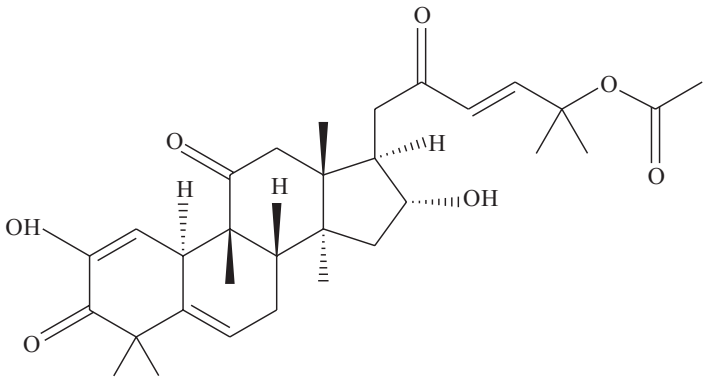


Fig. 10.10 Structure of cucurbitacin E

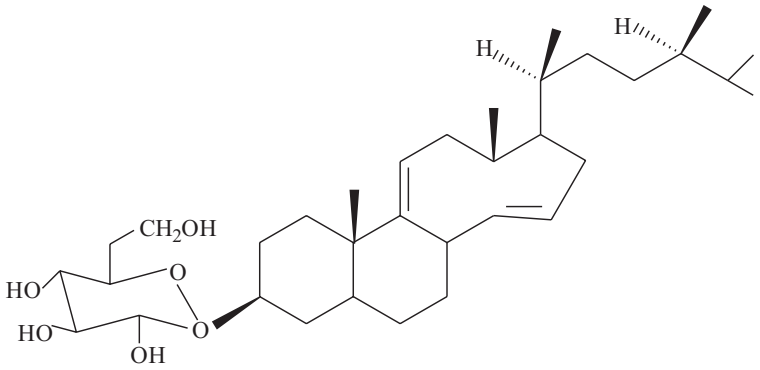


Fig. 10.11 Structure of bacosterol glycoside

Phenylethanoid Glycosides Monnierasides I–III and plantioside B (Chakravarty et al. 2002; Bhandari et al. 2007) and bacosterol glycoside (Bhandari et al. 2006) (Fig. 10.11)

10.4 Non-clinical Neuropharmacology

10.4.1 Adaptogenic Activity

Pretreatment with low dose of a standardized extract of *B. monniera* (40 mg/kg) significantly reversed changes in ulcer index and plasma aspartate aminotransferase only. On the other side, the pretreatment with higher dose significantly reversed chronic stress-induced changes in ulcer index, adrenal gland weight, aspartate aminotransferase and creatine kinase (Rai et al. 2003).

10.4.2 Anti-amnesic Activity

Bacopa monniera exerted 120 mg kg(−1) oral demonstrated anti-amnesic effect on diazepam (1.75 mg kg(−1) intraperitoneal)-induced anterograde amnesia in mice (Prabhakar et al. 2008).

10.4.3 Antianxiety Activity

Several authors have reported antianxiety or anxiolytic activity of *B. monnieri.* An earlier study reported antianxiety effect of *B. monniera* (Singh and Singh 1979). An experimental study reported anxiolytic activity of a standardized extract of *B. monniera* (bacoside A content 25.5 ± 0.8%) comparable to that of lorazepam (Bhattacharya and Ghosal 1998).

10.4.4 Antidopaminergic/Serotonergic Activity

N-Butanolic extract of *B. monnieri* containing bacoside A (bacoside A3, bacopaside II and bacopasaponin C) has been shown to reduce morphine hyperactivity and the elevated striatal dopamine and serotonin turnover. The researchers concluded that *N*-butanolic extract of *B. monnieri* might offer a possible treatment of morphine dependence (Rauf et al. 2012).

10.4.5 Antidepressant Activity

Methanolic extract of *B. monnieri* (20–40 mg kg^{-1}) given once daily for 5 days showed significant antidepressant activity in rats (Singh and Dhawan 1997). An experimental study reported potential antidepressant activity of a standardized extract of *B. monniera* standardized extract (bacoside A content 38.0 ± 0.9) comparable to that of imipramine (Sairam et al. 2002).

Bacopasides I and II and bacopasaponin C showed antidepressant effects on forced swimming and tail suspension in mice, respectively (Zhou et al. 2007). The methanolic extract of *B. monniera* showed significant antidepressant-like activity in forced swimming test, measurement of locomotor activity and tail suspension test in mice (Mannan et al. 2015).

10.4.6 Antiepileptic Activity

Just like the antianxiety or anxiolytic activities, several works have been reported highlighting the antiepileptic activity of *B. monniera*. *A brief experimental work reported* anticonvulsant activity of *Centella asiatica* and *B. monnieri* in animals (Sudha et al. 2005a, b, c). Neuroprotective activity of extract of *B. monniera* has been postulated in glutamate-mediated excitotoxicity during seizures and cognitive damage in pilocarpine-induced epilepsy (Amee et al. 2009).

10.4.7 The Cognition-Enhancing and Nootropic Activity

An aqueous suspension of an alcoholic extract of *B. monnieri* (40 mg/kg, p.o.) improved the performance of rats in various learning situations (Singh and Dhawan 1982). Researchers have suggested that bacosides cause membrane dephosphorylation, with a conjoined increase in protein and RNA turnover in specific brain areas.

The rats treated with the ethanolic extract of *B. monnieri* showed enhanced learning ability. The action was ascribed to active saponins, bacosides A and B (Singh and Dhawan 1997). Bacosides are supposed to enhance the protein kinase activity in the hippocampus which could be contributing factor to the nootropic activity

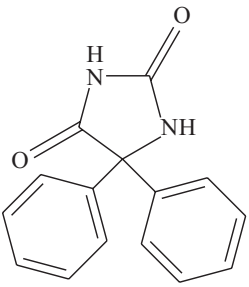


Fig. 10.12 Structure of phenytoin – antiepileptic agent

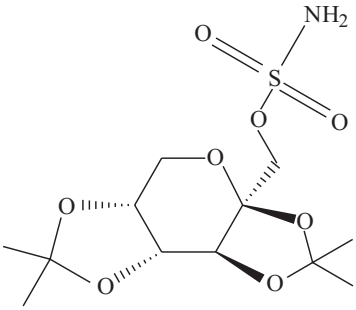


Fig. 10.13 Structure of topiramate – an anticonvulsant drug

(Singh and Dhawan 1997). *B. monniera* has been reported to have protective effect from phenytoin-induced cognitive deficit (Vohora et al. 2000) (Fig. 10.12).

Bacopaside I, bacopasaponin C and bacopaside XI isolated from the whole plant of *B. monniera* showed nootropic activity in the Morris water maze test and step-down test of scopolamine-induced memory impairment in mice (Zhou et al. 2009). The lipid extracts of *B. monnieri have comparable nootropic activity to the methanolic extract and* Ayurvedic ghrita (Lohidasan et al. 2009).

B. monnieri was given along with topiramate significantly reversed topiramate-induced impairment evident by decreased escape latency time, increased time spent in target quadrant and decreased acetylcholinesterase levels (Deval et al. 2011) (Fig. 10.13).

10.4.8 Neuroprotective Activity

Male Wistar rats were given AlCl3 (orally at a dose of 50 mg/kg/day in drinking water for 1 month) along with extract of *B. monniera* (40 mg/kg/day). The extract prevented lipid accumulation and protein damage from aluminium intake (Jyoti et al. 2007). Neuroprotective effect of *Bacopa monnieri* demonstrated neuroprotective activity on beta-amyloid-induced cell death in primary cortical culture (Limpeanchob et al. 2008).

10.5 Clinical Neuropharmacology

10.5.1 Anxiety Neurosis

A study observed 20% lower anxiety levels in patients suffering from anxiety neurosis given with *B. monniera* (Singh and Singh, 1980). An observational study, exploring utility of *B. monnieri* with the daily dose of 12 g, as syrup, showed significant improvements in anxiety concentration and memory in patients (Kidd 1999).

10.5.2 Attention-Deficit Disorder

Alcoholic extract of *B. monnieri* has also studied for its attention-deficit hyperactivity disorder in children with significant improvement in the areas of sentence repetition, logical memory and pair associative learning.

10.5.3 Human Memory

Several randomized, controlled human clinical trials have proved the cognition-enhancing and nootropic effects (Mukherjee and Dey 1966; Pase et al. 2012).

10.5.4 Acute Effects

A double-blind, placebo-controlled independent group design suggested that *B. monniera*, for the 300 mg, has no acute effects on cognitive functioning in normal healthy subjects (Nathan et al. 2001). An acute, double-blind, placebo-controlled crossover study reported adaptogenic and nootropic effects of 320 mg and 640 mg doses of *B. monnieri* (Benson et al. 2014).

10.5.5 Chronic Effects

In a double-blind placebo-controlled study, *B. monnieri* resulted in improved higher-order cognitive processes that are to an extreme degree dependent on learning and memory (Stough et al. 2001). In a double-blind, randomized, placebo-controlled study involving 76 adults aged between 40 and 65 years, *B. monnieri* decreases the rate of forgetting of newly acquired information (Roodenrijs et al. 2002).

A randomized, double-blind, placebo-controlled clinical trial with a placebo run-in of 6 weeks and a treatment period of 12 weeks showed that a standardized extract of *B. monnieri* 300 mg/day has potential for safely enhancing cognitive performance in ageing (Calabrese et al. 2008). A 90-day double-blind placebo-controlled randomized trial reported cognitive-enhancing effects in healthy humans after a 90-day

administration of the *B. monniera* extract (Stough et al. 2008). A special extract of *B. monniera* (CDRI08) has been reported to improve cognition in old-age people and in patients suffering from neurodegenerative diseases (Stough et al. 2013).

10.5.6 Epilepsy

In an uncontrolled study, the effect of *B. monniera* was studied in patients suffering from epilepsy and mental retardation. It was observed that a defatted extract of the dried plant was more potent than a decoction of the fresh plant. There was some suggestion that the treatment could reduce the incidence of fits and improve other symptoms (Mukherjee and Dey 1966).

10.6 A Note on Neuropharmacology of Bacosides

Bacosides A and B have facilitatory effect on mental retention capacity as they tend to improve responses with positive and negative reinforcement (Singh et al. 1988). Bacoside A has been shown to ameliorate epilepsy-associated behavioural deficits (Mathew et al. 2010).

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Neuropharmacology of *Acorus calamus* L.

11

11.1 Introduction

A. calamus L. (Araceae) is popularly known as vaca in Ayurveda. Sweet flag is the English name. *A. calamus* is native to Central Asia, India, southern Russia and Siberia.

11.2 Botany

A. calamus is a perennial plant. It is found in damp and swampy areas. The plant sends up leafy, grasslike stems from underground stalk. The stems grow up to 5 ft high. Halfway up the stem, each leaf bears a 2–4-in.-long fleshy cylindrical flower stalk, consisting of many tiny yellow-brown flowers (Motley 1994).

11.3 Chemistry

A. calamus contains volatile oil (1.5%–3.5%). β-Asarone is the major phenylpropene of the oil. β-Asarone is also known as cis-isoasarone. In addition, α-asarone is also present (McGaw LJ et al. 2002) (Figs. 11.1 and 11.2).

The content of β-asarone in tetraploid plant oil is 90–96%. The content of β-asarone in tetraploid plant oil is 5%. β-Asarone is absent in diploid plant (Rost and Bos 1979).

The plant contains sesquiterpenes like calamerone, calamendiol and isocalamendiol (Fig. 11.3).

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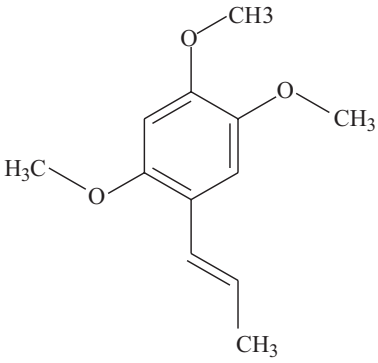

Fig. 11.1 Structure of α-asarone

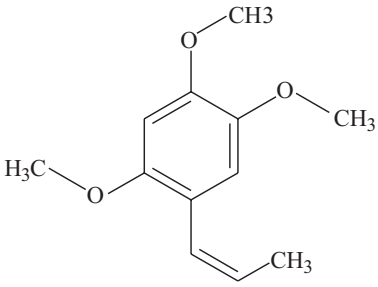

Fig. 11.2 Structure of β-asarone

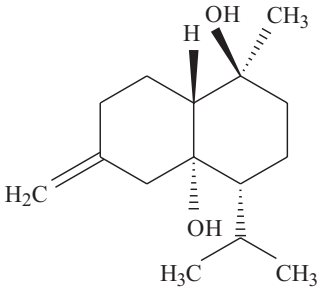

Fig. 11.3 Structure of calamendiol

11.4 Neuropharmacology of *A. calamus* Extract

11.4.1 Anti-anxiety

Seventy percent hydro-ethanolic extract of *A. calamus* significantly attenuated anxiety-related disorders. Further, it significantly caused reduction in stress phenomenon and resulting depression (Bhattacharyya et al. 2011).

11.4.2 Antidepressant

In established models of depression, the behavioural deficit was prevented very well as by *A. calamus* as compared to stressed group (Tripathi and Singh 2010).

11.4.3 Antiepileptic

In study, *A. calamus* has preventive effect on chloride-induced epilepsy. Modulation of the antioxidant enzymes has been explained as a possible mechanism (Hazra et al. 2007).

11.4.4 Antistress

Ethyl acetate and methanolic extracts of *A. calamus* showed protective activity against the changes in the brain of the rat caused by noise stress (Manikandan et al. 2005).

11.4.5 CNS Activity

An ethanolic extract of the rhizomes of *A. calamus* has similar profile to α-asarone as far as CNS effects are concerned. However, the extract differed from α-asarone in the following aspects:

- Amphetamine toxicity in aggregated mice
- Apomorphine- and isolation-induced aggressive behaviour
- Behavioural despair syndrome in forced swimming
- Responses to electroshock (Vohora et al. 1990)

11.4.6 Neuroprotective

A. calamus demonstrated potential activity against acrylamide-induced neurotoxicity (Shukla et al. 2002). *A. calamus* demonstrated neuroprotective effect against middle cerebral artery occlusion-induced ischaemia in rats (Shukla et al. 2006).

In a rat model, hydroalcoholic extract of *A. calamus* and pregabalin offered protective effect in vincristine-induced painful neuropathy (Muthuraman et al. 2011) (Fig. 11.4).

An extract of *A. calamus* rich in saponin showed ameliorative effect in chronic constriction injury-induced neuropathic pain (Muthuraman and Singh 2012).

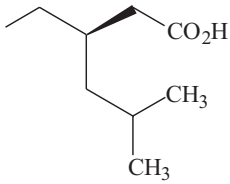

Fig. 11.4 Structure of pregabalin

11.5 Neuropharmacology of Essential Oil

The steam volatile fraction obtained from the underground parts has been reported to hypnotic and hypothermic activity and increases the tonic seizures (Dandiya et al. 1959)**.** Combination of hersaponin and acorus oil is reported to have impact on the noradrenaline and serotonin contents in the brain of the rat (Malhotra et al. 1961).

An exploratory study threw light on neuropharmacological actions of acorus oil (Dhalla and Bhattacharya 1968). An initial experimental study reported antiepileptic activity of essential oil of *A. calamus* (Khare and Sharma 1982). The observations of an experimental study showed the essential oil having significant acetylcholinesterase inhibitory activity (Mukherjee et al. 2007).

11.6 Neuropharmacology of α- and β-Asarone

α-Asarone and β-asarone were reported to have pharmacodynamic actions similar to reputed tranquilizers (Sharma et al. 1961). A few pharmacological actions of α-asarone and β-asarone on central nervous system have been observed (Dandiya and Sharma 1962). The potentiating effect of α-asarone and β-asarone on reserpine and of chlorpromazine has no relation to serotonin concentration (Dandiya and Sharma 1963).

α-Asarone reduced spontaneous motor activity and anxiety without dulling the perception in rats. Further, in monkeys, α-asarone showed a prolonged calming effect (Dandiya and Menon 1964). A study reported positive impact of asarone on experimentally induced conflict neurosis in rats (Chak and Sharma 1965). It has been postulated that the sedative effect of α-asarone is dependent on the depression of the ergotropic division of the hypothalamus (Menon and Dandiya 1967).

Sedative activity of β-asarone has been reported (Zanoli et al. 1998). α-Asarone offered protection in different regions of the brain against noise stress-induced changes. Antioxidant property of β-asarone was the possible mechanism involved (Manikandan and Devi 2005). Asarones have been reported to have acetylcholinesterase-inhibiting activity (Houghton et al. 2006; Mukherjee et al. 2007).

β-Asarone resulted in improvement in cognition by having suppressive action on neuronal apoptosis in the beta-amyloid hippocampus injection rats warranting possible use in Alzheimer's disease (Geng et al. 2010). α-Asarone is reported to improve striatal cholinergic function and locomotor hyperactivity in Fmr1 knockout mice (Qiu et al. 2016).

11.6.1 Clinical Studies with *A. calamus*

A clinical study reported efficacy of *A. calamus* in treating the patients suffering from depression (Tripathi and Singh 1995). A study evaluating efficacy of α-asarone in 18 patients diagnosed with status epilepticus reported beneficial effects (Bannerjee 1967).

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Neuropharmacology of *Celastrus paniculatus* Willd.

12

12.1 Introduction

Celastrus paniculatus Willd. syn. *C. multiflorus* Roxb. (Celastraceae) is a hardy shrub that grows in a wide variety of climates and environments (Krishnamurthy 1993). The plant is native to the Indian continent but is known to grow wildly in Australia, China, Taiwan, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Nepal, Sri Lanka, Thailand and Vietnam as well as in many of the Pacific islands (Singh et al. 1996).

12.2 Botany

C. paniculatus is a deciduous climbing shrub that can grow to a very large size. The base stem of this shrub will grow up to 25 cm in diameter and produce many woody branches that will cling to surrounding flora for support. The leaves are oblong-elliptic, and the flowers are unisexual. The seeds, which grow inside capsules, number from anywhere between 1 and 6 seeds per capsule and yield dark-brown oil, known as *Celastrus* oil or Malkangni oil (Satakopan and Gaitonde 1960).

12.3 Traditional Medicinal Uses

For thousands of years, Ayurveda medicine has advocated the use of seeds of *C. paniculatus* for their potential medicinal properties. The plant has been used in the treatment of several diseases, but nootropic or brain tonic property is the noteworthy property. In addition, *C. paniculatus* is an effective appetizer and emetic (Bhattacharjee 2000).

The oil expressed from the seeds is a valued remedy for improving intellect and memory. Further, the oil has been employed for the treatment of beriberi and malaria (Chopra 1956).

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According to Graeco-Arabic Yunani (Unani) medicine, the oil expressed from the seeds was effectively used in the treatment of convalescence, mental confusion, bronchial asthma, headache and arthritis. In Unani medicine, an effective balm was prepared from the oil and used as aphrodisiac in men (Ravishankar and Shukla 2007).

12.4 Phytochemistry

12.4.1 Fixed Oil (Sengupta and Bhargava 2006)

12.4.2 Alkaloids

Paniculatine A, paniculatine B, celastrine, celapanine, celapanigine, celapagine and wifornine F (Basu and Pabrai 2006; Yasu et al. 2006) (Figs. 12.1 and 12.2).

12.4.3 Polyalcohols

Malangunin, malkanginnol, malkanguniol and paniculatadiol (Patel et al. 1995).

12.4.4 Triterpenoid

Pristimerin (Sang et al. 2005) (Fig. 12.3).

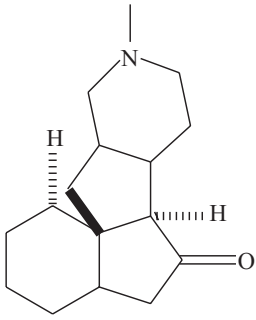

Fig. 12.1 Structure of celastrine

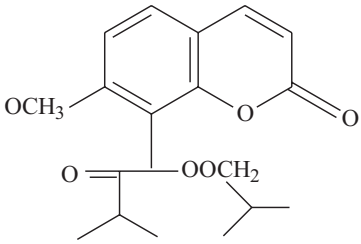

Fig. 12.2 Structure of paniculatine

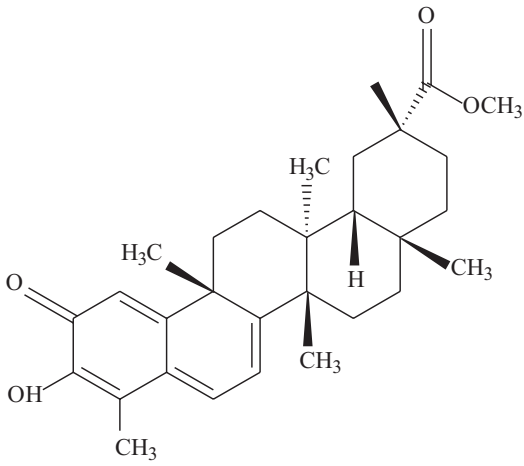

Fig. 12.3 Structure of pristimerin

12.5 Non-clinical Neuropharmacology

12.5.1 Anti-amnesic Activity

The oil resulted in an overall decrease in the turnover of neurotransmitters, including dopamine, norepinephrine and serotonin. The retention ability of the rats treated with oil improved significantly as compared to the saline-administrated controls (Nalini et al. 1995).

Young adult rats treated with *C. paniculatus* (50, 200 or 400 mg/kg) for 14 days showed complete reversal of scopolamine-induced task performance deficit (Gattu et al. 1997).

12.5.2 Antianxiety Activity

C. paniculatus seeds at doses of 1 and 1.5 g/kg demonstrated significant antianxiety activity and were well-tolerated. The non-sedative potential and reversal of buspirone (an anxiolytic drug)-induced behavioural changes throw light at involvement of the serotonergic pathway as possible mechanism for antianxiety activity (Rajkumar et al. 2007) (Fig. 12.4).

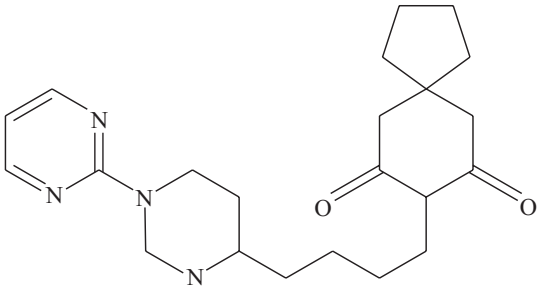

Fig. 12.4 Structure of buspirone

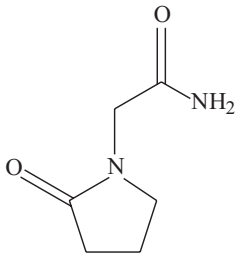

Fig. 12.5 Structure of piracetam

12.5.3 Nootropic Activity

In elevated plus-maze and sodium nitrite-induced amnesia model, the water extract of the seed of *C. paniculatus* resulted in statistically significant enhancement in memory process as compared to piracetam (a cerebral enhancer) in mice and rats (Bhanumathy et al. 2010) (Fig. 12.5).

12.5.4 Neuroprotective Activity

A study reported the effect of *C. paniculatus* seed extract on the brain of albino rats (Bidwai et al. 1987) The water-soluble seed extract of *C. paniculatus* and organic extracts have neuroprotective activity on neuronal cells of the rat forebrain against hydrogen peroxide-induced oxidative injury (Godkar et al. 2003) and glutamate-induced injury (Godkar et al. 2006).

The neuronal cells pretreated with *C. paniculatus* seed oil resulted in attenuation of death caused by glutamate. The neuroprotective activity of the seed oil has been linked to modulation of the function of the glutamate receptor (Praful and Sushil 2004; Godkar et al. 2004).

12.5.5 Tranquilizing Activity

A fraction of *C. paniculatus* oil having potential tranquilizing activity has been reported (Sheth et al. 1963).

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Phytopharmacology of Indian Nootropic *Convolvulus pluricaulis*

13

13.1 Introduction

Convolvulus is a genus of about 250 species of flowering plants in the bindweed family Convolvulaceae, with a cosmopolitan distribution (Feinbrun-Dothan 1978). *C. pluricaulis* occurs in temperate and subtropical regions and is a perennial herb and stoloniferous rhizome. Leaves are flat, scabrous and liner green with prominent nerves. Flowers are 10-20 flowered pale or purplish with three stamens. Its fruit is a nut, which is oblong, trigonous, stramineous and stiptate (Madhavan et al. 2008; Karandikar and Satakapan 1959).

13.2 Phytochemistry

An active alkaloid, sankhpuspine, has been isolated from *C. pluricaulis*. Volatile oil has been obtained by steam distillation of the fresh plant (Basu and Dandiya 2006; Bisht and Singh 1978).

13.3 Actions and Therapeutics

In Ayurveda, *C. pluricaulis* is used as Medhya Rasayana (nootropic or memory booster) (Dandiya and Chopra 1970). In India, syrup of the whole plant is a popular remedy for boosting childhood memory.

Therapeutically *C. pluricaulis* is considered to be tonic, alterative and febrifuge. It is used to treat fever, nervous debility and memory loss. The whole plant is used medicinally in the form of decoction with cumin and milk in syphilis and scrofula (Singh 2005).

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_13

13.4 Preclinical Pharmacology

13.4.1 Anti-anxiety Activity

Ethyl acetate fractions of ethanolic extract of *C. pluricaulis* at a dose of 100 mg/kg, administered by oral route, demonstrated significant anti-anxiety activity. The activity was evident by increase in the time spent in open arms and the number of open arms entries as compared to the control group. The same fraction in a dose of 200 mg/kg administered by oral route demonstrated significantly reduced neuromuscular coordination indicative of the muscle relaxant activity (Nahata et al. 2009).

13.4.2 Antidepressant Activity

A. In albino rats, the alcoholic extract of *C. pluricaulis* at a dose of 100 mg/kg potentiated the barbiturate. However, the activity was weak as compared to diazepam and *Centella asiatica* (Shukla 1980).

B. The chloroform fraction of the total ethanolic extract of *C. pluricaulis* at doses of 50 and 100 mg/kg caused significant reduction in the immobility time in forced swim as well as tail suspension tests. The efficacy of the chloroform fraction was comparable to antidepressants like imipramine and fluoxetine. Further, the chloroform fraction caused reversal of reserpine-induced extension of immobility period in forced swim test.

Prazosin (diuretic), sulpiride (a typical antipsychotic) and p-chlorophenylalanine (inhibitor of tryptophan hydroxylase) significantly attenuated the chloroform fraction-induced antidepressant-like effect in tail suspension test (Dhingra and Valecha 2007) (Figs. 13.1, 13.2 and 13.3).

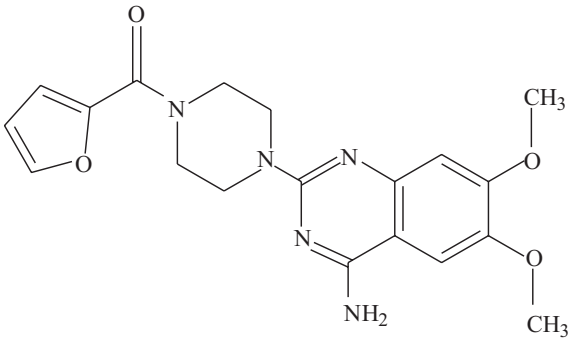

Fig. 13.1 Structure of prazosin

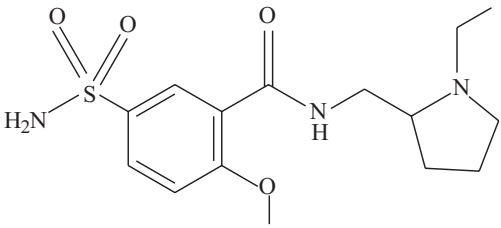

Fig. 13.2 Structure of sulpiride

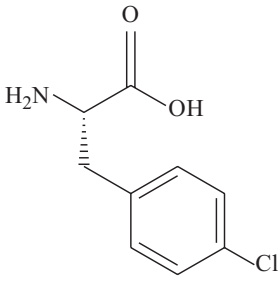

Fig. 13.3 Structure of *p*-chlorophenylalanine

13.4.3 Antiepileptic Activity

The alcoholic extract of *C. pluricaulis* abolished spontaneous motor activity and fighting response, but did not affect the escape response; electrically induced convulsive seizures and tremorine-induced tremors were antagonized by the extract (Mulchandani et al. 1995).

13.4.4 CNS Depressant Activity

The methanol extract of the whole plant of *C. pluricaulis* was found to produce alterations in the general behaviour pattern, reduction in spontaneous motor activity, hypothermia, potentiation of pentobarbitone sleeping time, reduction in exploratory behavioural pattern and suppression of aggressive behaviour. The extract also showed an inhibitory effect on conditioned avoidance response and antagonism to amphetamine toxicity (Pawar et al. 2001).

13.4.5 Analgesic Activity

The extract of *C. pluricaulis* reduced the fighting behaviour in mice. The action was devoid of analgesic activity but potentiated morphine analgesia (Sharma et al. 1965).

13.4.6 Nootropic Activity

Ethanolic extract of *C. pluricaulis* enhanced neuropeptide synthesis in the brains of laboratory animals. The brain protein was increased, indicating increased memory and acquisition efficiency (Sharma et al. 1965).

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Neuropharmacology of *Rhodiola rosea* L. 14

14.1 Introduction

R. rosea (Crassulaceae) is commonly known as roseroot (Sagalov 1983). The plant is native to dry, high-altitude regions of the northern hemisphere. *R. rosea* is better described as adaptogen in herbal medicine. *R. rosea* is a herbaceous perennial plant with a thick rhizome. *R. rosea* is one of the best-known herbal remedies for fatigue (Tharakan and Manyam 2006).

14.2 Chemistry

Phenylpropanoids Rosavin, rosin, rosarin and rosiridin (Tolonen et al. 2003) (Figs. 14.1, 14.2, 14.3 and 14.4)

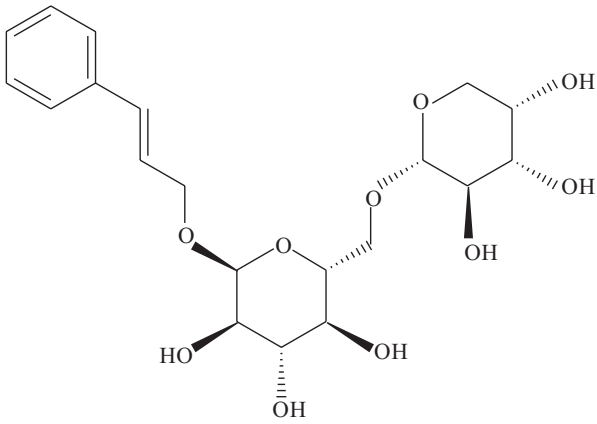


Fig. 14.1 Structure of rosavin

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_14

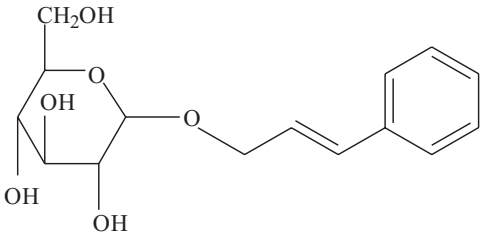


Fig. 14.2 Structure of rosin

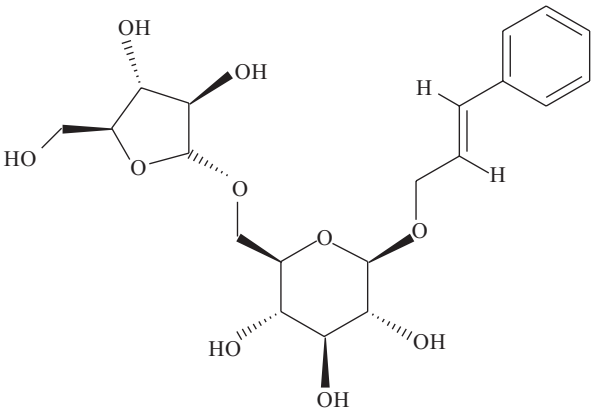


Fig. 14.3 Structure of rosarin

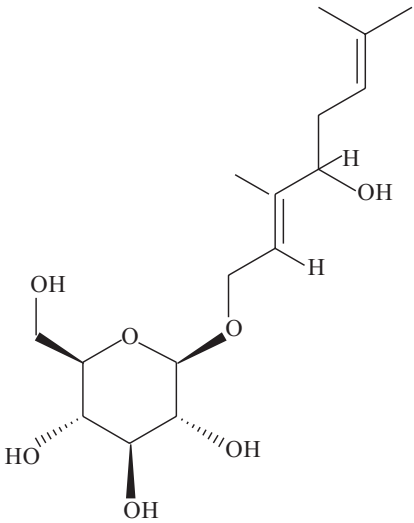


Fig. 14.4 Structure of rosiridin

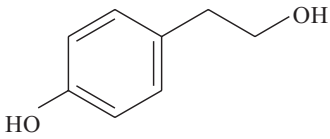


Fig. 14.5 Structure of tyrosol

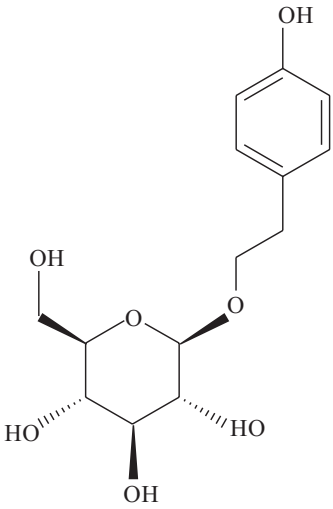


Fig. 14.6 Structure of salidroside (rhodioloside)

Phenylethanol Derivatives Salidroside (rhodioloside) (Thieme 1969) and tyrosol (Panossian et al. 2010) (Figs. 14.5 and 14.6)

Flavonoids Acetylrodalgin, rodiolin, rodionin, rodiosin and tricin (Figs. 14.7, 14.8 and 14.9)

Monoterpenes Rosiridol and rosaridin

Triterpenes Daucosterol and beta-sitosterol

Phenolic Acids Chlorogenic acid, hydroxycinnamic acid and gallic acid

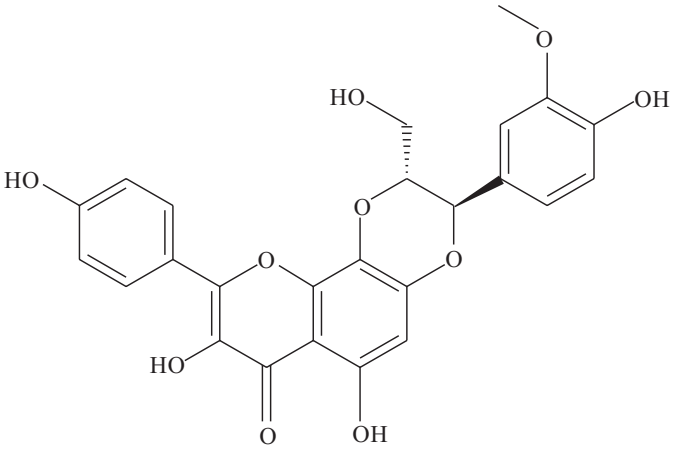


Fig. 14.7 Structure of rodiolin

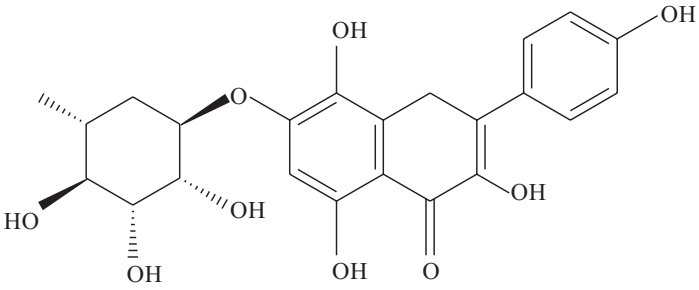
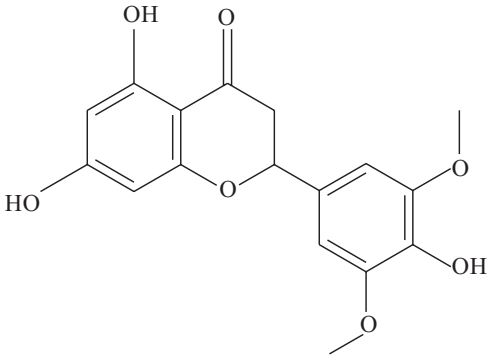


Fig. 14.8 Structure of rodionin

Fig. 14.9 Structure of tricin



14.3 Non-clinical Neuropharmacology

14.3.1 Adaptogenic

The hydroalcoholic extract of *R. rosea* containing 3% rosavin and 1% salidroside had significant adaptogenic and central nervous system effects (Perfumi and Mattioli 2007). *Rhodiola rosea* L. extract has been reported to reduce stress- and corticotrophin-releasing factor-induced anorexia in rats (Mattioli and Perfumi 2007).

R. rosea extract has a potent inhibiting effect on the behavioural and physiological changes by chronic exposure to stress induced by agents (Mattioli et al. 2009). *R. rosea* extract has been reported to increase the non-specific resistance and activate the process of adaptogensis (Andreeva et al. 2013).

14.3.2 Antianxiety

In the elevated plus maze, an alcoholic extract of *R. rosea* roots demonstrated dose-dependent anxiolytic activity. However, the study failed to elicit the exact mechanism behind the antianxiety activity (Cayer et al. 2013).

14.3.3 Antidepressant

The extract of *R. rosea* promoted the differentiation and proliferation of neural stem cells in the hippocampus of the rats suffering from depression (Qin et al. 2008). Low-dose *R. rosea* in a low dose increased the body weight and sucrose intake in rats suffering from depression (Chen et al. 2008). The methanol and water extracts of *R. rosea* have been reported to inhibit MAO-A and MAO-B (van Diermen et al. 2009). An animal study has shown that the extract of *R. rosea* improved levels of 5-hydroxytryptamine (serotonin) in hippocampus in depressive rats (Chen et al. 2009).

A study justified the association of the antidepressant mechanism of rhodioloside with anti-inflammatory activity and the regulation of the hypothalamic-pituitary-adrenal axis activity (Yang et al. 2014). The up-regulation of the monoaminergic system activity and anti-inflammatory activity has been explained as the possible mechanism behind the antidepressant-like effect of rhodioloside (Zhang et al. 2016). A short-term study has shown genuine utility of *R. rosea* extract in terms of the safety profile in comparison to standard antidepressants (Amsterdam and Panossian 2016).

14.3.4 CNS Activity

Alcohol aqueous extract from the roots of *R. rosea* improved learning and retention in rats after 24 h. However, the extract lacked substantial effect on the process of learning and memory (Petkov et al. 1986). Salidroside showed preventive effect on cognitive dysfunction caused by chronic cerebral hypoperfusion in rats (Yan et al. 2015). Beneficial effect of *R. rosea* extracts was reported in rats with scopolamine-induced memory impairment (Vasileva et al. 2016).

14.3.5 Neuroprotective

Salidroside demonstrated protective effect against oxidative stress-induced apoptosis (Zhang et al. 2007). Salidroside has potential neuroprotective effect against β-amyloid-induced oxidative stress in SH-SY5Y human neuroblastoma cells (Zhang et al. 2010).

Neuroprotective effects of salidroside and tyrosol have been reported against focal cerebral ischaemia in vivo and H2O2-induced neurotoxicity in vitro (Shi et al. 2012). Similarly, both the compounds demonstrated protective effect on H9c2 cells from ischaemia-/reperfusion-induced apoptosis (Sun et al. 2012).

Salidroside has been reported to promote regeneration of the peripheral nerve in rats followed by crush injury to the sciatic nerve (Sheng et al. 2013). The neuroprotective action of salidroside has association with induction of early growth response genes resulting in inhibition of Bax/Bcl-xl-related apoptosis (Lai et al. 2015).

Intravenous administration of p-tyrosol in a dose of 20 mg/kg resulted in increased survival and caused a reduction in the neurological deficit after GCI. Further, it reduced damage to the neurons in the hippocampus and lipid peroxidation in brain tissue in animals (Atochin et al. 2016).

14.3.6 Clinical Neuropharmacology

14.3.6.1 Anxiety

In a pilot study, significant improvement in symptoms of generalized anxiety disorder warranting further clinical trials has been reported (Bystritsky et al. 2008).

14.3.6.2 Depression

In a randomized, placebo-controlled trial, a standardized extract of *R. rosea* in dosages ranging from 340 to 680 mg/day for 6 weeks demonstrated antidepressive activity in patients diagnosed with mild to moderate depression (Darbinyan et al. 2007).

In a clinical study, a standardized extract of *R. rosea* has been reported to be beneficial in the treatment of patients diagnosed with mild to moderate depression (Ross 2014b). In a randomized, placebo-controlled trial, the antidepressant effect of *R. rosea* was less in comparison to sertraline. However, the herbal drug was better tolerated, and significantly fewer side events were noted (Mao et al. 2015).

14.3.6.3 Stress-Related Fatigue

In a randomized, placebo-controlled trial, repeated administration of *R. rosea* extract showed an antifatigue effect in patients suffering from fatigue syndrome (Olsson et al. 2009). In a clinical study, a standardized extract of *R. rosea* has been reported to be beneficial in treating stress-related fatigue (Ross 2014a).

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Neuropharmacology of *Salvia miltiorrhiza* Bunge (Danshen)

15

15.1 Introduction

S. miltiorrhiza (Lamiaceae) finds wide use in traditional Chinese medicine and is popularly known as red sage. The Chinese name of the medicinal plant is danshen. The plant is native to China and Japan. The roots are used in medicine.

15.2 Botany

S. miltiorrhiza is a deciduous perennial plant. The branching stems are 30–60 cm tall, with widely spaced leaves that are both simple and divided. The inflorescence is covered with hairs and sticky glands. Flowers grow in whorls, with light-purple to lavender-blue corollas.

15.3 Traditional Medicinal Uses

S. miltiorrhiza is used in the treatment of chronic renal failure in traditional Chinese medicine (TCM). The plant finds application in the treatment of angina pectoris, hyperlipidaemia and myocardial infarction.

15.4 Chemistry

Depside Salvianolic acid B (Lian-Niang et al. 1984)

Diterpenoid Quinine Miltirone (Hayashi et al. 1971; Chang et al. 1991)

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Quinone Tanshinone I, tanshinone IIA and tanshinone IIB (Lian-Niang et al. 1984) (Figs. 15.1, 15.2, 15.3, 15.4 and 15.5)

15.5 Neuropharmacology

Miltirone is an active central benzodiazepine receptor ligand (Chang et al. 1991). Miltirone has the strong potency as far as inhibition of the binding of [3H]flunitrazepam to central benzodiazepine receptors is concerned (Lee et al. 1991).

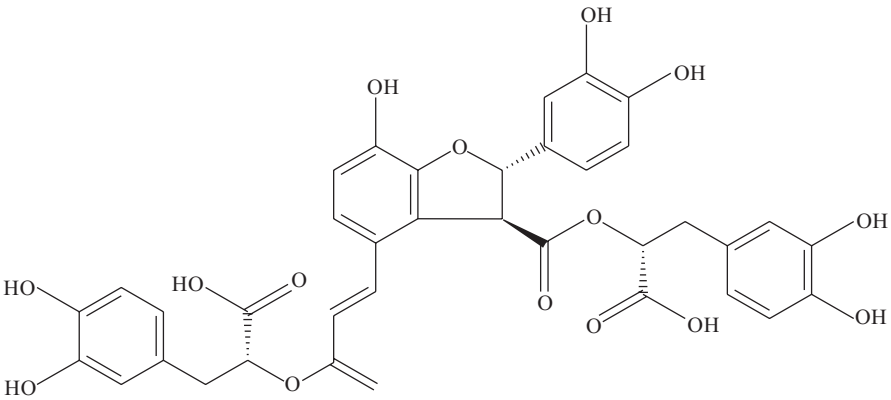


Fig. 15.1 Structure of salvianolic acid B

Fig. 15.2 Structure of tanshinone I

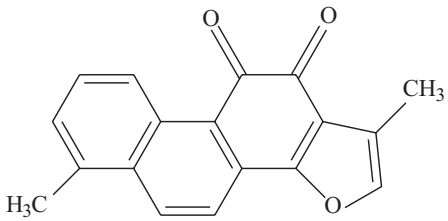
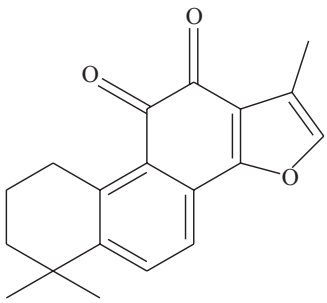


Fig. 15.3 Structure of tanshinone IIA



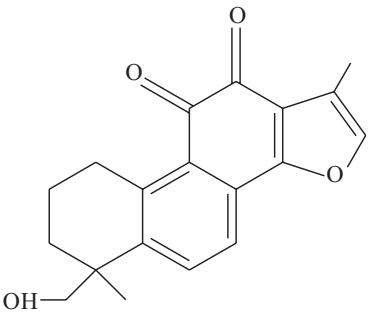


Fig. 15.4 Structure of tanshinone IIB

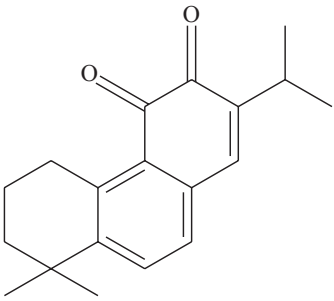


Fig. 15.5 Structure of miltirone

15.5.1 Anti-addiction Activity

IDN 5082, a standardized extract of *S. miltiorrhiza*, delayed the acquisition of alcohol drinking behaviour in rats (Brunetti et al. 2003). *S. miltiorrhiza* caused inhibition of superoxide generation by activated rat microglias. Further, it stimulated dopamine release as done by amphetamine in vitro. However, therapeutic use in treating drug addiction needs to be explored (Koo et al. 2004).

It has been suggested that miltirone ameliorates the effects associated with withdrawal of long-term administration of ethanol or of other positive modulators of the GABAA receptor (Mostallino et al. 2004). Miltirone has been identified as possible candidate responsible for the reducing effect of *S. miltiorrhiza* extracts on alcohol intake in different animal models with alcohol consumption in excess (Colombo et al. 2006).

15.5.2 Anti-Alzheimer's Activity

Cryptotanshinone has been reported to ameliorate scopolamine-induced amnesia in Morris water maze task (Wong et al. 2010a). Cryptotanshinone and dihydrotanshinone cause non-competitive inhibition of human acetylcholinesterase. Further, both cause an uncompetitive inhibition of human butyrylcholinesterase (Wong et al. 2010b) (Figs. 15.6 and 15.7).

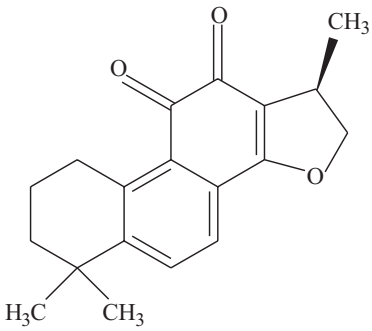


Fig. 15.6 Structure of cryptotanshinone

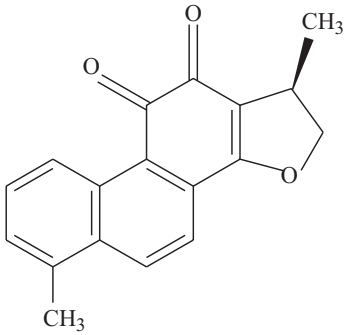


Fig. 15.7 Structure of dihydrotanshinone

The root extract of *S. miltiorrhiza* caused strong inhibition of brain acetylcholinesterase and butyrylcholinesterase justifying further investigation as possible treatment of Alzheimer's disease (Ozarowski et al. 2017).

15.5.3 Anti-Parkinson's Activity

Tanshinone IIA had preventive effect on nigrostriatal dopaminergic neuronal loss. Tanshinone inhibited NADPH oxidase and nitric oxide synthase in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease (Ren et al. 2015). Tanshinone I has been reported to selectively suppress the pro-inflammatory gene expression in activated microglia and prevent nigrostriatal dopaminergic neurodegeneration in a mouse model of Parkinson's disease (Wang et al. 2015).

15.5.4 Cerebroprotective Activity

The treatment with *S. miltiorrhiza* resulted in decreased lipid peroxidation in reperfusion injury (Kuang et al. 1996a). In four-vessel occlusion rat model, pretreatment with *S. miltiorrhiza* resulted in normalizing the levels of cerebral nitric oxide (Kuang et al. 1996b). As per results of a study, *S. miltiorrhiza* has potential in reducing the

area of cerebral infarction in ischaemia-reperfusion injured rats (Lo et al. 2003). Tanshinone IIB has been reported to be effective in reducing stroke-induced brain damage (Yu et al. 2007).

Salvianolic acid B has been reported to stimulate neurogenesis process both in subgranular and subventricular zone after brain ischaemia (Zhong et al. 2007). The neuroprotective activity of tanshinone IIB is due to inhibition of neuronal apoptosis in vitro (Yu et al. 2008).

Inhibition of mitogen-activated protein kinase pathway by salvianolic acid B has been explained as a possible protective effect on the blood-brain barrier (Li et al. 2010). The cerebroprotective activity of salvianolic acid A has been linked to the inhibition of granulocyte adherence (Jiang et al. 2011).

Tanshinone IIA has been reported to attenuate the extent of brain oedema formation in response to ischaemia injury in rats, partly protective effect on the blood-brain barrier (Tang et al. 2010). The polysaccharides from the roots of *S. miltiorrhiza* have potential cerebroprotective activity on cerebral ischaemia/reperfusion injury in rats, and antioxidant effect has been explained as a possible mode of action (Tu et al. 2013).

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Neuropharmacology of *Withania somnifera* Dunal.

16

16.1 Introduction

W. somnifera belongs to family Solanaceae. The Ayurvedic synonyms for the plant include Ashwagandha, Avarohaka, Balya, Gokarna, Turangahva, Vajikari, Varada, Varahakarni and Vrsa. In English, the plant is known as winter cherry. *W. somnifera* is found in India.

W. somnifera is a perennial herb covered with hairs. It has tap root; stem is herbaceous above and woody below. Leaves are in unequal pairs; flowers are greenish or yellowish; fruit berry becomes red on ripening.

Chemical Composition Alkaloids (ashwagandhine, ashwagandhinine, anagrine, anaferine, cuscohygrine, hygrine, isopelletriene, pseudopelletriene, 3-tropyltigloate, tropine and withasomnine), withanolides (ashwagandhanolide, withaferin A, 27-deoxy-withaferin A, withanone, withacoagin, coagulin, withasomidienone, 3ß-hydroxy-2,3-dihydro withanolide F, withaniol, withaferinil, withanolide D, and withanolide E), sitoindosides IX and X, proteins and amino acids (Khanna et al. 1962; Das et al. 1964; Lavie et al. 1965, 1975; Bharat et al. 1970; Ghosal et al. 1988) (Figs. 16.1, 16.2, 16.3, 16.4, 16.5 and 16.6).

Therapeutics *W. somnifera* is used in the treatment of depression, hypertension, general debility, oligozoospermia, stress, premature ejaculation and leucorrhoea. In asthma, ash of *W. somnifera* is given with honey and vegetable oil. Root and leaves are used in medicine. Ashwagandhadi churna and Ashwagandharishta are important formulations based on the plant.

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_16

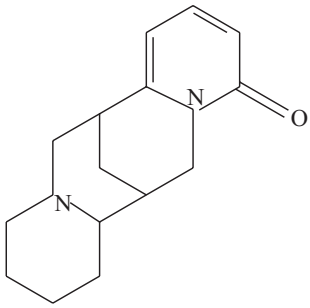


Fig. 16.1 Structure of anagyrine

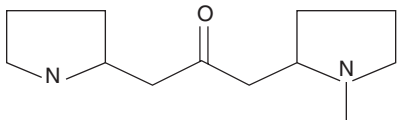


Fig. 16.2 Structure of cuscohygrine

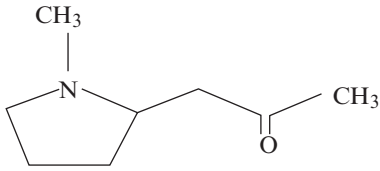


Fig. 16.3 Structure of hygrine

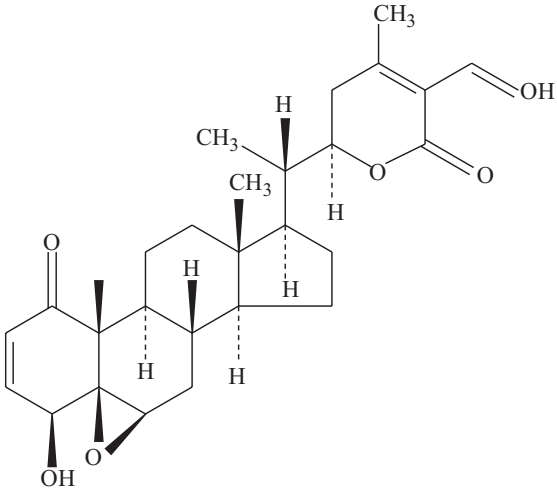


Fig. 16.4 Structure of withaferin A

Fig. 16.5 Structure of 27-deoxy-withaferin A

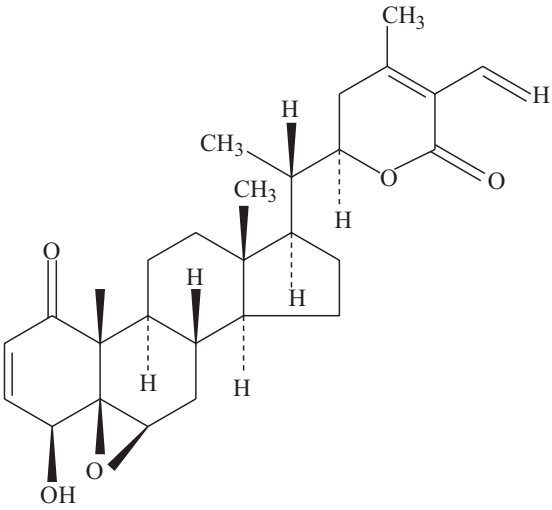
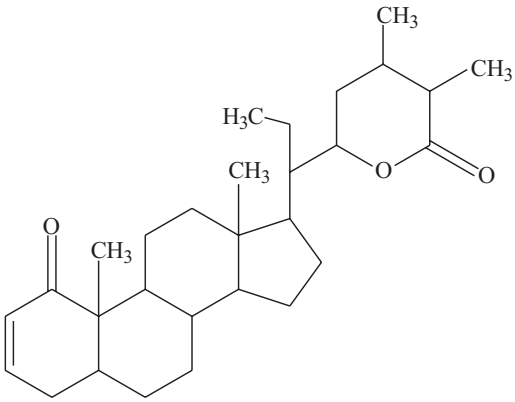


Fig. 16.6 Structure of withanolide D



16.2 Non-clinical Neuropharmacology

16.2.1 Anti-Alzheimer's Activity

Withanoside IV ameliorated Abeta(25–35)-induced neurodegeneration in Alzheimer's disease. Sominone, a steroidal sapogenin, has been shown to be the active principle after metabolism of the withanolide (Kuboyama et al. 2006).

16.2.2 Anxiolytic-Antidepressant Activity

Glycowithanolides from the root of *W. somnifera*, in the elevated plus-maze test, produced an anxiolytic effect, comparable to that of lorazepam. The compounds in

the forced swim-induced tests exhibited an antidepressant effect, comparable with that induced by imipramine (Bhattacharya et al. 2000). Possible involvement of nitric oxide has been elaborated in the antidepressant-like effect of *W. somnifera* in male mice Attari et al. 2016).

16.2.3 Anticataleptic Activity

W. somnifera extract has been reported to be more efficacious than scopolamine in causing reversal of haloperidol-induced catalepsy. The antioxidant activity of *W. somnifera* extract has been explained as a possible mechanism (Nair et al. 2008).

16.2.4 Antiparkinson's Activity

Rats were pretreated with 100, 200 and 300 mg/kg b.w. of the *W. somnifera* extract orally for 3 weeks demonstrated that the extract protects the neuronal injury in Parkinson's disease induced by 6-hydroxydopamine (Ahmad et al. 2005). A study proved that withdrawal from *W. somnifera* does not retain anticataleptic activity and that it may be a suitable adjuvant in the treatment of Parkinson's disease instead of caffeine (Kasture et al. 2009).

16.2.5 Antistress Activity

In chronic stress-induced changes in the rat's brain, glycowithanolides demonstrated an antioxidant activity, thereby justifying the role of *W. somnifera* as antistress agent (Bhattacharya et al. 2001).

16.2.6 CNS Activity

A study explained the effect of the total extract, total alkaloids (ashwagandholine) and acetone and alcohol- and water-soluble alkaloidal fractions on the central nervous system (Malhotra et al. 1960, 1965; Prasad and Malhotra 1968).

16.2.7 Cognition-Enhancing Activity

W. somnifera root extract has preventive effect on reserpine-induced orofacial dyskinesia and cognitive dysfunction. The cognition-enhancing activity of the medicinal plant has been linked to potential antioxidant activity (Naidu et al. 2006). In a fat-based obesity model, the leaf of *W. somnifera* has been reported to improve cognitive dysfunction by enhancement of plasticity of the hippocampus (Manchanda and Kaur 2017).

16.2.8 Neuritic Regeneration Activity

Withanolide A, other withanolides and a methanolic extract of *W. somnifera* have potential neuritic regeneration and dendrite formation activity (Tohda et al. 2000; Zhao et al. 2002; Kuboyama et al. 2002, 2005).

16.2.9 Neuroprotective Activity

W. somnifera root powder extract significantly reduced (80%) the number of degenerating cells in hippocampal subregions of female albino rat (Jain et al. 2001). *W. somnifera* root extract in doses of 100 and 200 mg/kg demonstrated dose-dependent neuroprotective activity against 3-nitropropionic acid-induced behavioural changes in an animal model of Huntington's disease.

W. somnifera root extract has been reported to ameliorate memory impairment induced by hypobaric hypoxia in rats (Baitharu et al. 2013). The neuroprotective activity of withanolide A is based on modulation of biosynthesis of glutathione in the hippocampus during hypoxia (Baitharu et al. 2014). The aqueous leaf extract of *W. somnifera* has potential role to offer in neuroprotection in acute stress of sleep deprivation (Manchanda et al. 2017).

16.3 Clinical Neuropharmacology

16.3.1 Cognition Enhancement

A randomized placebo-controlled study in 35 patients reported a utility of an extract of *W. somnifera* for enhancing cognitive dysfunction in bipolar disorder (Chengappa et al. 2013). In healthy human participants, a standardized aqueous extract of *W. somnifera* has been reported to cause improvement in cognitive and psychomotor performance (Pingali et al. 2014).

A pilot study reported efficacy of *W. somnifera* root extract in cognition and memory enhancement in adults with mild cognitive impairment (Choudhary et al. 2017).

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Neuropharmacology of *Nardostachys jatamansi* DC.

17

17.1 Introduction

Nardostachys jatamansi DC. is an important plant of the family Valerianaceae. Indian spikenard is the common name of the plant and is found in Himalayas. *N. jatamansi* is a perennial herb. The rhizomes occur in short pieces and have dark-grey colour and typical smell. Leaves are sessile and ovate. Flowers are dark pink in colour.

17.2 Traditional Medicinal Use

In Ayurvedic system of medicine, *N. jatamansi* is frequently used in the treatment of nervous headache, excitement, menopausal symptoms, flatulence, epilepsy and intestinal colic.

17.3 Phytochemistry

The roots of the plant contain essential oil, which is rich in sesquiterpenes and coumarins.

17.3.1 Sesquiterpenes

Jatamansone or valeranone (Fig.) is the principal sesquiterpene. Other sesquiterpenes include nardostachone (Fig.), dihydrojatamansin, jatamansinone, jatamansinol, oroseolol, oroselone, seselin, valeranal, nardostachyin, nardosinone, spirojatamol, jatamols A and B, calarenol, seychellene, seychelane and jatamansic acid (Biswas 1963, Sastry et al. 1967; Rücker and Tautges 1974; Rucker et al.

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_17

1978a; Bagchi et al. 1990; Bagchi et al. 1991; Harigaya et al. 2000; Chatterjee et al. 2005a, b) (Figs. 17.1, 17.2, 17.3, 17.4, 17.5, 17.6, 17.7, 17.8, 17.9, 17.10 and 17.11).

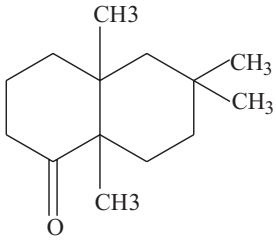

Fig. 17.1 Structure of jatamansone (valeranone)

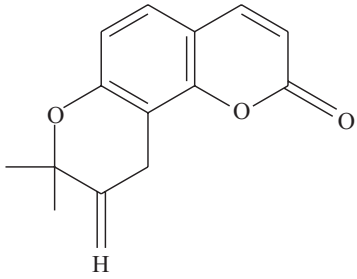

Fig. 17.2 Structure of jatamansinol

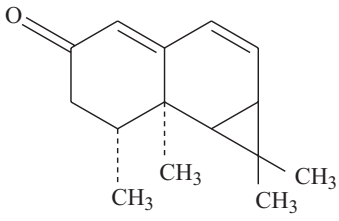

Fig. 17.3 Structure of nardostachone

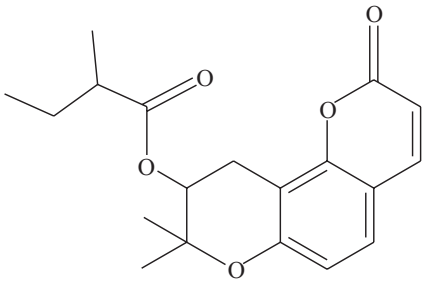

Fig. 17.4 Structure of dihydrojatamansone

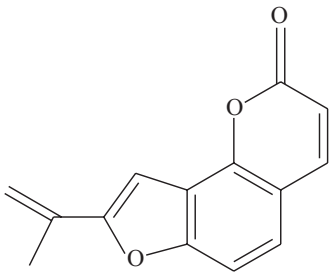

Fig. 17.5 Structure of oroselone

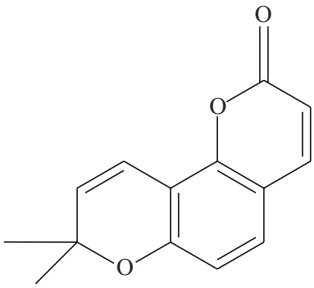

Fig. 17.6 Structure of seselin

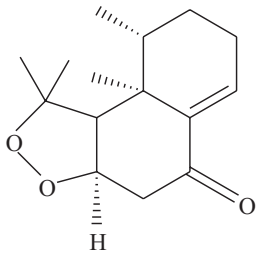

Fig. 17.7 Structure of nardosinone

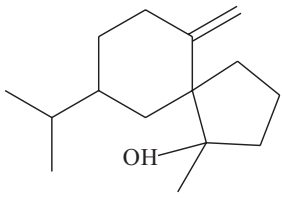

Fig. 17.8 Structure of spirojatamol

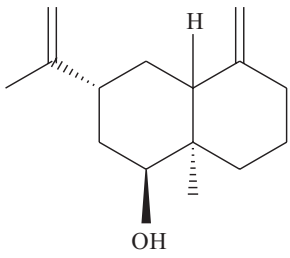

Fig. 17.9 Structure of jatamol A

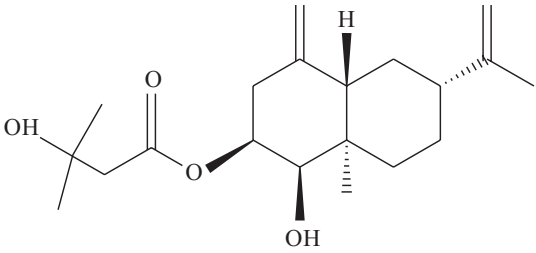

Fig. 17.10 Structure of jatamol B

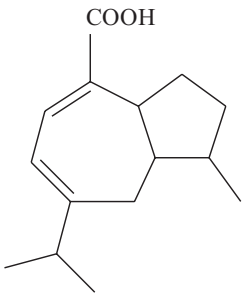

Fig. 17.11 Structure of jatamansic acid

17.3.2 Coumarins

Jatamansin or xanthogalin (Rucker et al. 1978a)

17.3.3 Sesquiterpene Acid

Nardin and nardol (Chatterjee et al. 2005a) (Figs. 17.12 and 17.13)

17.3.4 Pyranocoumarin

2', 2'-Dimethyl-3'-methoxy-3', 4'-dihydropyranocoumarin (Chatterjee et al. 2005a, b) (Fig. 17.14).

17.3.5 Alkaloid

Actinidine (Fig. 17.15).

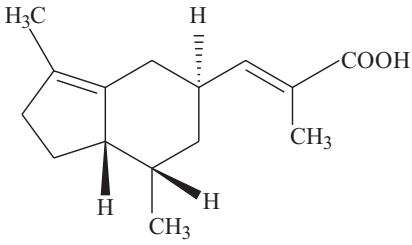

Fig. 17.12 Structure of nardin

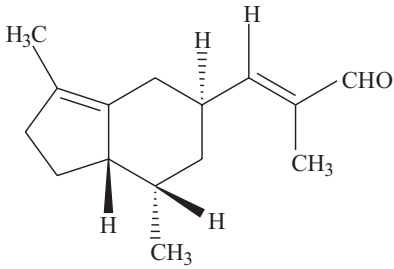

Fig. 17.13 Structure of nardol

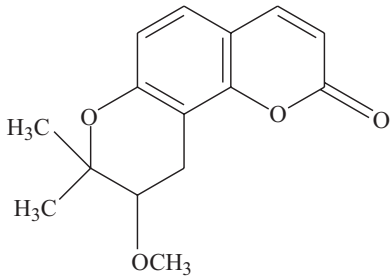

Fig. 17.14 Structure of 2′, 2′-dimethyl-3′-methoxy-3′, 4′-dihydropyranocoumarin

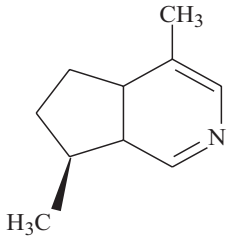

Fig. 17.15 Structure of actinidine

17.4 Non-clinical Neuropharmacology

17.4.1 Anticonvulsant Activity

The ethanolic extract of the roots of *N. jatamansi* caused a significant increase in the seizure threshold against maximal electroshock seizure model as evident by a decrease in the extension/flexion ratio. Pretreatment of rats with phenytoin in combination with *N. jatamansi* root extract caused a significant increase in the protective index of phenytoin from 3.63 to 13.18 (Rao et al. 2005).

17.4.2 Antidepressant Activity

A 15-day treatment with an alcoholic root extract of *N. jatamansi* caused an overall increase in the levels of central monoamines and inhibitory amino acids, including a change in the levels of serotonin, 5-hydroxyindoleacetic acid, gamma-aminobutyric acid and taurine in rat brain (Prabhu et al. 1994).

17.4.3 Anti-Parkinson's Activity

A significant decrease in the level of dopamine and its metabolites and an increase in the number of dopaminergic D2 receptors in striatum were observed after 6-hydroxydopamine injection, and both were significantly recovered following *N. jatamansi* treatment (Ahmad et al. 2006).

17.4.4 Memory-Enhancing Activity

The ethanolic extract of *N. jatamansi* in a dose of 200 mg/kg significantly improved learning and memory in young mice and also reversed the amnesia induced by diazepam at a dose of 1 mg/kg, i.p., and scopolamine at a dose of 0.4 mg/kg, i.p. Antioxidant activity has been postulated as a possible mode of action behind the memory-enhancing activity (Joshi and Parle 2006).

17.4.5 Neuroprotective Activity

The rats pretreated with an alcoholic extract of *N. jatamansi* at a dose of 250 mg/kg were protected against focal ischemia resulting from occlusion of the middle cerebral artery. An increase in the glutathione content coupled with inhibition of the lipid peroxidation has been explained as a possible mode of action behind the neuroprotective activity (Salim et al. 2003).

17.4.6 Nootropic Activity

Results indicated that methanolic extracts of *N. jatamansi* are more active in inhibiting acetylcholinesterase than water extracts. The IC (50) values for methanolic and successive water extracts were 47.21 mug/ml (Vinutha 2007).

17.5 Non-clinical Neuropharmacology of Jatamansone (Valeranone)

Jatamansone has anticonvulsant activity without exhibiting neuroleptic characteristics (Arora and Arora 1963). Jatamansone exhibited anticonvulsant activity against electric shock and gastroprotective actions (Arora et al. 1962).

17.6 Clinical Neuropharmacology of Jatamansone

In a clinical study involving hyperkinetic children, efficacy of jatamansone, D-amphetamine and chlorpromazine was compared. Jatamansone and amphetamine both resulted in a significant improvement in behaviour. Amphetamine was, however, superior as far as reduction in aggressiveness and restlessness was concerned. Further, fewer side effects were recorded for jatamansone as compared to the rest of the drugs (Gupta and Vermani 1968).

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Neuropharmacology of Nutritional Supplements

18

Folic Acid So far, few randomized trials are known for the role of folic acid or folate in depression. Folate added to antidepressant drug treatment offered limited evidence that folate has potential role in depression (Zhao et al. 2011). Some studies have reported utility of folic acid in treating depression (Watanabe et al. 2012) (Fig. 18.1).

Tryptophan Tryptophan is the biological precursor to the monoamine neurotransmitter, serotonin. Serotonin is found to be deficient in depressive states, particularly with suicidal pattern. Several well-controlled studies have thrown light on the fact that serum levels of L-tryptophan are abnormally low in some depressive illness. Further, the studies emphasize that the presence of the amino acid is necessary for the effectiveness of antidepressants (Soh and Walter 2011) (Fig. 18.2).

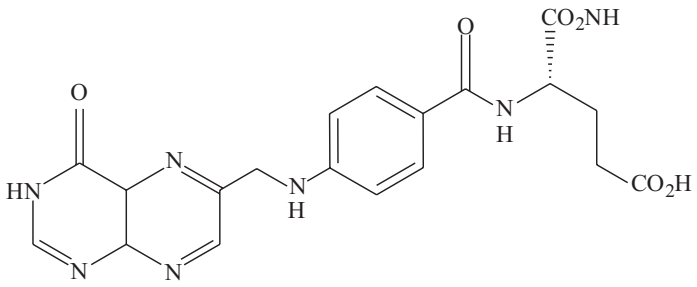


Fig. 18.1 Structure of folic acid

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_18

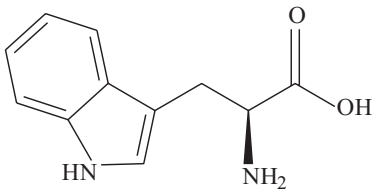


Fig. 18.2 Structure of tryptophan

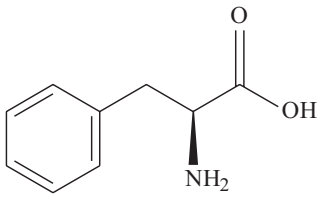


Fig. 18.3 Structure of phenylalanine

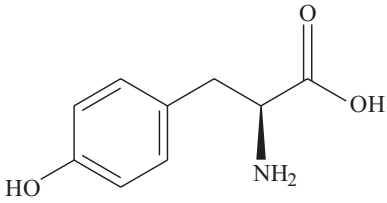


Fig. 18.4 Structure of tyrosine

Phenylalanine and Tyrosine Phenylalanine is one of the essential amino acids and serves as a precursor to several cofactors (Figs. 18.3 and 18.4).

Tyrosine (4-hydroxyphenylalanine) is produced from phenylalanine and is a precursor to the catecholamine, norepinephrine (Fig. 18.5).

When metabolic augmentation of iodine and tyrosine takes place, thyroid hormones are produced. The decrease in levels of thyroid hormones is a contributing factor to depression. Phenylethylamine (a central nervous system stimulant in humans) is derived from phenylalanine. Phenylethylamine is known as a mood enhancer (Fig. 18.6).

Studies of LPA used to treat depression found that it was an effective antidepressant for some individuals (Beckmann et al. 1977; Beckmann and Ludolph 1978; Beckmann et al. 1979).

***S*-Adenosyl Methionine (SAMe)** SAMe is a naturally occurring compound found in almost every tissue and fluid in the body. The production of SAMe in the human body occurs from methionine, the essential amino acid. The compound plays a role in the metabolism of vital neurotransmitters like serotonin, noradrenaline and dopamine (Chavez 2000) (Fig. 18.7).

Studies have shown SAMe to be safe and effective in treating depression with very few side effects. It is believed that the conversion of methionine to SAMe is

Fig. 18.5 Structure of norepinephrine

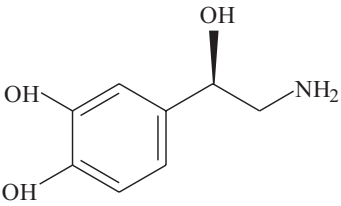


Fig. 18.6 Structure of phenylethylamine

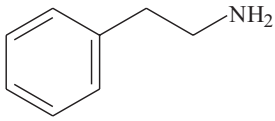
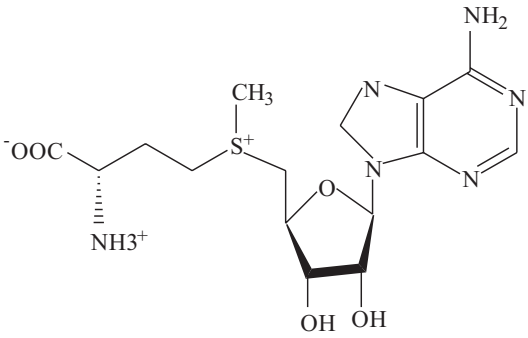


Fig. 18.7 Structure of *S*-adenosyl methionine



slowed in depressed individuals (Galizia et al. 2016). The results of two multicentre studies showed that the antidepressant efficacy of 1600 mg SAMe/d orally and 400 mg SAMe/d intramuscularly was comparable with that of 150 mg imipramine/d orally, but SAMe was significantly better tolerated (Delle et al. 2002).

Results of a 6-week open trial involving 30 adult patients diagnosed with major depressive disorder and consuming 800–1600 mg of SAMe along with venlafaxine demonstrated that further placebo-controlled trials are required (Alpert et al. 2004). In a 6-week randomized, double-blind, placebo-controlled trial, SAMe of 800–1600 mg/d failed to cause a significant increase in total homocysteine levels proving lack of toxicity (Mischoulon et al. 2012).

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Neuropharmacology of *Valeriana* Genus 19

19.1 *Valeriana officinalis* L.

Garden valerian and garden heliotrope are the common name for this species. The plant is native to certain parts of Asia and Europe and a member of Valerianaceae. However, it has been introduced into North America. It is worthwhile to note that the amino acid, valine, has been named after *V. officinalis* (Fig. 19.1).

In traditional medicine and herbal medicine, *V. officinalis* is a reputed remedy for anxiety and insomnia (Manson 1928; Kieswetter and Muller 1958). Valerian tincture was widely described for therapeutic purpose and in the treatment of vegetative dystonias and related disorders (Dymchenko 1969).

19.1.1 Chemistry

Alkaloids: actinidine, chatinine, shyanthine, valerianine, and valerine

19.1.1.1 Valepotriates (Figs. 19.2 and 19.3)

19.1.1.2 Organic Compounds (Figs. 19.4 and 19.5)

19.1.1.3 Sesquiterpenes (Figs. 19.6, 19.7 and 19.8)

19.1.2 Non-clinical Neuropharmacology

19.1.2.1 Antidepressant

The use of *V. officinalis* in the treatment of autonomic dysfunctions has been elaborated (Peters 1953; Boeters 1969; Haas 1996). Aqueous and hydroalcoholic extracts of *V. officinalis* displaced [3H] muscimol binding. The effect has been correlated with GABA content (Cavadas et al. 1995).

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_19

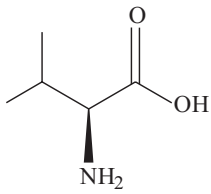

Fig. 19.1 Structure of valine

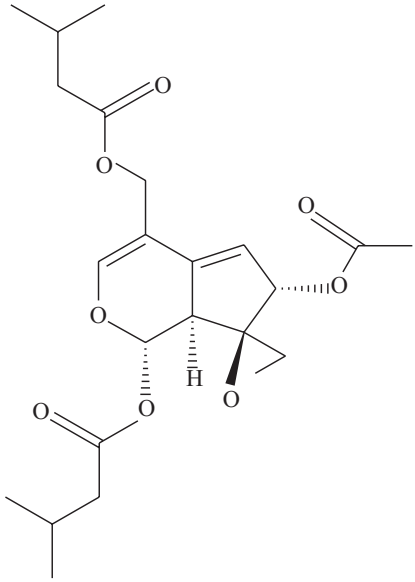

Fig. 19.2 Structure of isovaltrate

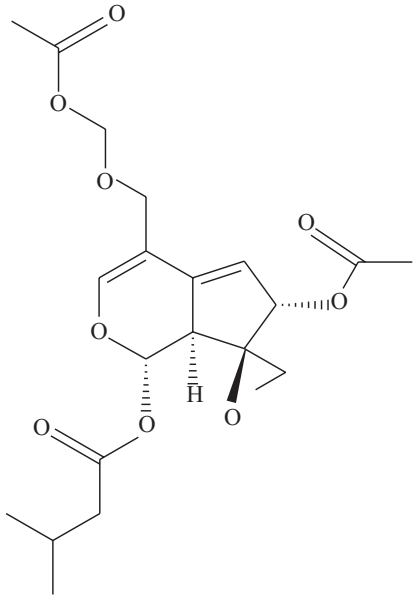

Fig. 19.3 Structure of valtrate

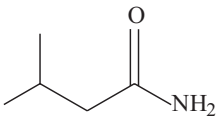

Fig. 19.4 Structure of isovaleramide

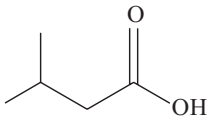

Fig. 19.5 Structure of isovaleric acid (3-methylbutanoic acid)

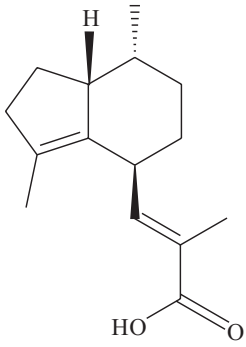

Fig. 19.6 Structure of valerenic acid

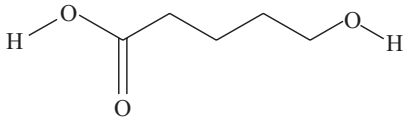

Fig. 19.7 Structure of 5-hydroxyvalerenic acid

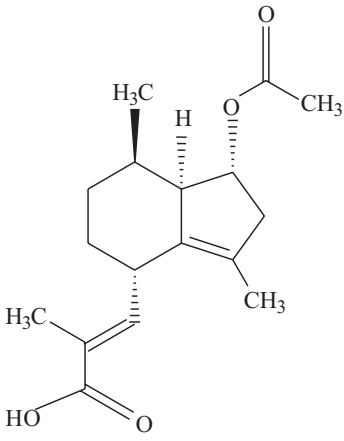

Fig. 19.8 Structure of acetovalerenic acid

The effect of *V. officinalis* extracts is not only confined to GABAA receptors but with interaction at other presynaptic components of GABAergic neurons also (Ortiz et al. 1999). The hydroalcoholic extract of *V. officinalis* has antidepressant-like activity in ovalbumin-sensitized rats (Neamati et al. 2014).

19.1.2.2 Anxiolytic

An in vivo study has shown GABAA receptors as substrate for the anxiolytic action of valerenic acid, the sesquiterpene *of V. officinalis* root extracts (Benke et al. 2009). *V. officinalis* and the sesquiterpene in the volatile oil, valerenic acid, demonstrated potential anxiolytic properties in the zebra fish. The interaction of *V. officinalis* with glutamate receptors is proposed to be the mode of action behind the anxiolytic activity (Del Valle-Mojica and Ortíz 2012).

V. officinalis extract having high amount of valerenic acid and low amount of acetoxy valerenic acid demonstrated anxiolytic activity (Felgentreff et al. 2012). The anxiolytic activity of is based on modulation of GABAA receptors, and valerenic acid is responsible for the activity. Addition of acetoxy valerenic acid abolishes the anxiolytic activity of valerenic acid (Becker et al. 2014).

19.1.2.3 Neuroprotective

A neuroprotective activity of *V. officinalis* extract against Abeta toxicity has been reported (Malva et al. 2004). *V. officinalis* extract having potential antioxidant activity is beneficial in reducing the incidence of complications associated with oxidative stress (Sudati et al. 2009).

19.1.3 Clinical Neuropharmacology

19.1.3.1 Cognitive Dysfunction

Based on a study, it was concluded that the cognitive state of patients receiving the valerian group was better than that in the placebo group after coronary artery bypass graft surgery (Hassani et al. 2015).

19.1.3.2 Obsessive-Compulsive Disorder

In a randomized double-blind study, patients receiving extract of *V. officinalis* in a dose of 765 mg/day for 8 weeks reported significant antiobsessive and compulsive effects (Pakseresht et al. 2011).

19.1.3.3 Insomnia

A pilot study reported that *V. officinalis* extract resulted in an increase in slow-wave sleep in subjects with low baseline values (Schulz et al. 1994). A study on 23 outpatient symptomatic Hispanic volunteers consuming 470 mg of *V. officinalis* root reported improved sleep (Dominguez et al. 2000). In yet another study, treatment with *V. officinalis* extract has positive impact on the structure of the sleep and perception in patients suffering from insomnia (Donath et al. 2000).

19.2 *Valeriana alliariifolia* Adams

This species is found in Greece and West Asia. It contains essential oil and valepotriates (valiracyl) (Hölzl and Koch 1984). The neurotropic effects of valiracyl are related to increased level of the GABA inhibition mediator and decreased intensity of bioenergetic processes in the brain (Dunaev et al. 1987).

19.3 *Valeriana edulis* ssp. *procera*

This species is commonly known as "valeriana mexicana". The plant finds wide application in Mexican traditional medicine for the treatment of anxiety and insomnia. Valepotriates are the main active constituents of the plant (Castillo et al. 2002). A dose-dependent anticonvulsant and anxiolytic-like effect of *V. edulis* has been demonstrated (Oliva et al. 2004). A randomized trial reported usefulness of *Valeriana edulis* on sleep difficulties in children suffering from intellectual deficits (Francis and Dempster 2002).

19.4 *Valeriana fauriei* Briq.

V. fauriei is found in northeast of China, South Korea and Japan. The plant is a rich source of sesquiterpenes (Zhang et al. 2006). A methanolic extract of the roots of *V. fauriei* demonstrated antidepressant activity in mice. The extract was fractionation of the extract yielded alpha-kessyl alcohol as the antidepressant constituent (Oshima et al. 1995). In vivo antidepressant activity of sesquiterpenes from the roots has been reported (Liu et al. 2012) (Fig. 19.9).

19.5 *Valeriana glechomifolia* Meyer

V. glechomifolia is native from southern Brazil. Valepotriates are the main active principles (Salles et al. 2000). Valepotriates from the plant demonstrated antidepressant-like activity. An interaction of the valepotriates with dopaminergic

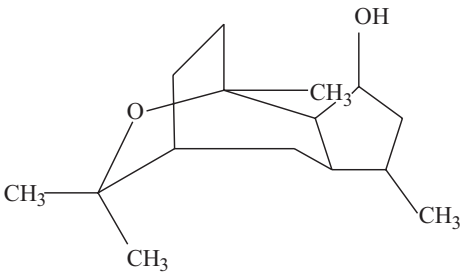

Fig. 19.9 Structure of alpha-kessyl alcohol

and noradrenergic neurotransmission contributes the antidepressant activity (Müller et al. 2012). The valepotriates have been reported to have beneficial effect in depression associated with inflammation (Müller et al. 2015).

19.6 *Valeriana wallichii* D.C.

This plant is popularly known as Tagara in Ayurveda and Indian valerian in English. It is common in Northwest Himalayas. As far as action on the nervous system is concerned, *V. wallichii* has a nervine and sedative property. In Ayurveda, it is successfully used in the treatment of hysteria, hypochondria, nervousness and emotional states. The essential oil content of the plant is relatively higher as compared to *V. officinalis.* Valepotriates, 6-methylapigenin, linarin-isovalerianate and isovaleryl glucoside have been identified as major phytochemicals (Thies 1968; Wasowski et al. 2002).

6-Methylapigenin isolated from the plant has been identified as a competitive ligand for the brain GABAA receptors (Wasowski et al. 2002). *V. wallichii* root extract has been reported to improve sleep quality. Further, it modulates monoamine level in the rat's brain (Sahu et al. 2012).*V. wallichii* rhizome extract has neuroprotective activity against the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in C57BL/6 mice (Sridharan et al. 2015).

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Neuropharmacology of Curcumin

20

20.1 Detailed Chemical Composition of Turmeric

Turmeric contains protein (6.3%), fat (5.1%), minerals (3.5%), carbohydrates (69.4%) and moisture (13.1%). The essential oil (5.8%) obtained by steam distillation of rhizomes has α-phellandrene or p-mentha-1,5-diene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpenes (53%) (Figs. 20.1, 20.2, 20.3, 20.4 and 20.5).

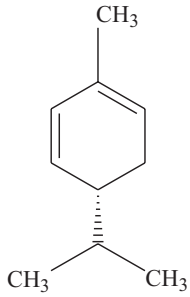

Fig. 20.1 Structure of phellandrene or p-mentha-1,5-diene

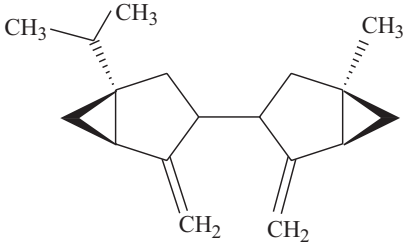

Fig. 20.2 Structure of sabinene

A. S. Saroya, J. Singh, *Pharmacotherapeutic Potential of Natural Products in Neurological Disorders*, https://doi.org/10.1007/978-981-13-0289-3_20

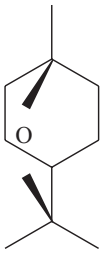

Fig. 20.3 Structure of 1,8-cineole

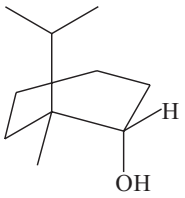

Fig. 20.4 Structure of borneol

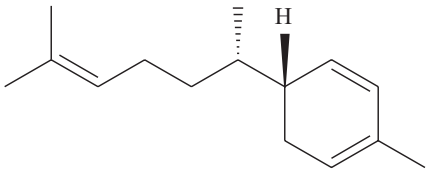

Fig. 20.5 Structure of zingiberene

Curcumin (diferuloylmethane) (3–4%) is responsible for the yellow colour and comprises curcumin I (94%), curcumin II (6%) and curcumin III (0.3%). Demethoxy and bisdemethoxy derivatives of curcumin have also been isolated (Figs. 20.6, 20.7 and 20.8).

20.2 Non-clinical Neuropharmacology

20.2.1 Anti-Alzheimer's Activity

Curcumin has been reported to cause reduction in oxidative damage and pathology of amyloid in an Alzheimer transgenic mouse (Lim et al. 2001). The analogues of curcumin have been reported to bind amyloid in Alzheimer's disease post-mortem brain tissue (Veldman et al. 2016).

20.2.2 Antidepressant Activity

A study reported monoamine oxidase inhibitory activity of curcumin in rats explaining the antidepressant activity (Xu et al. 2005a). In yet another study involving rats, curcumin demonstrated antidepressant activity in the forced swim and the bilateral olfactory bulbectomy models of depression. Involvement of the central

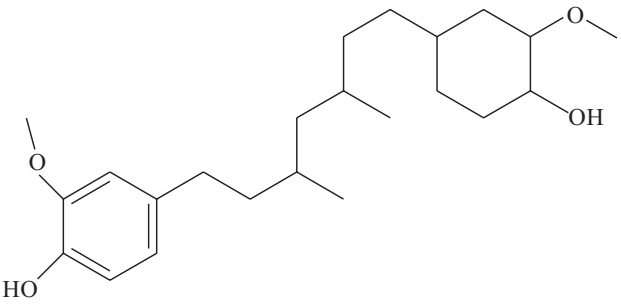

Fig. 20.6 Structure of curcumin

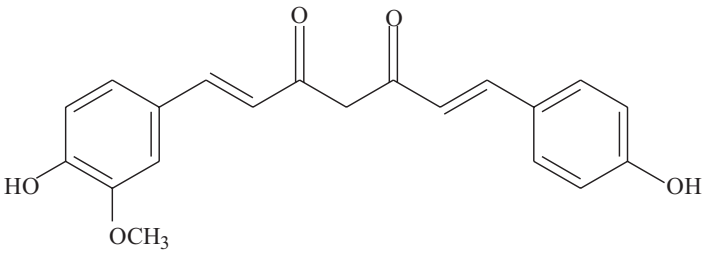

Fig. 20.7 Structure of demethoxycurcumin

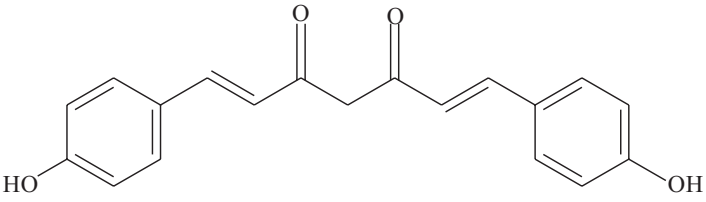

Fig. 20.8 Structure of bisdemethoxycurcumin

monoaminergic neurotransmitter systems might be the contributing factor behind the antidepressant activity (Xu et al. 2005b).

Involvement of 5-HT1 and 5-HT2 receptors has been linked to the antidepressant activity of curcumin in the forced swimming test (Wang et al. 2008). In rats, curcumin exerted antidepressant-like effects and reversed the insulin resistance and metabolic abnormalities induced by chronic mild stress (Shen et al. 2017). Curcumin has been shown to reverse corticosterone-induced depressive-like behaviour and decrease brain-derived neurotrophic factor levels in rats (Huang et al. 2011).

A randomized, double-blind, placebo-controlled trial reported efficacy of curcumin and saffron/curcumin combination in patients diagnosed with major depression (Lopresti and Drummond 2017).

20.2.3 Neuroprotective

Curcumin has potential neuroprotective activity on ethanol-induced brain damage (Rajakrishnan et al. 1999). Curcumin has been reported to have protective effect against ischemia/reperfusion insult in the forebrain of the rat. The antioxidant activity of curcumin has been explained as a possible mechanism (Ghoneim et al. 2002). In rats, curcumin has potential protective activity against lead neurotoxicity (Shukla et al. 2003).

Immediate as well as delayed treatment with curcumin has also preventive activity against ischemia-induced neuronal damage in the forebrain and oxidative insult in the hippocampus of the rat (Al-Omar et al. 2006). Curcumin has been reported to attenuate 3-nitropropionic acid-induced neurotoxicity (Kumar et al. 2007).

Curcumin has been reported to attenuate bupivacaine-induced neurotoxicity in SH-SY5Y cells via activation of the Akt signalling pathway (Fan et al. 2016). Curcumin offers neuroprotection against alcohol-induced hippocampal neurodegeneration via activation of cAMP response element-binding protein-brain-derived neurotrophic factor signalling pathway (Motaghinejad et al. 2017). Curcumin in association with piperine has neuroprotective mechanism against 6-hydroxy quinolinic acid and dopamine-induced neurotoxicity in rats (Singh and Kumar 2017).

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