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REVIEW ARTICLE

Patented Antiinflammatory Plant Drug Development from Traditional Medicine

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Patents secured on antiinflammatory plant drugs derived from 38 plants are reviewed. An attempt has been made to compare the modern and traditional use of plant drugs and to establish the relevance of folk claims in developing modern drugs. The role of plant botanicals such as polysaccharides, terpenes, curcuminoids, alkaloids, etc. in alleviating inflammatory diseases including arthritis, rheumatism, acne skin allergy and ulcers is highlighted. Chemicals that alleviate swelling are derived from plants including grape, boswellia, turmeric, devil's claw and some essential oils such as clove, eucalyptus, rosemary, lavender, mint, myrrh, millefolia and pine have been patented and used as mixed formulations. Plants containing polysaccharides are the most potent in curing inflammatory diseases. Copyright © 2004 John Wiley & Sons, Ltd.

Keywords: reviews; antiinflammatory activity; plant drug patents; inatural product patents; inflammation management; rheumatism; polysaccharides; essential oils.

INTRODUCTION

Medicinal plants have played a major role as a source of pharmacologically active substances. The search for new antiinflammatory drugs from nature continues, although the mere isolation of a new antiinflammatory agent is unlikely to lead to a drug unless, and until, its mechanism of action is known. Antiinflammatory agents are highly diversified, and diseases such as haemorrhoids, rheumatism and body ache, acne, skin problems, ulcers etc. have an inflammatory component. An acute inflammation is more severe and short lived, while chronic inflammation can extend and cause other illness, so broad-spectrum antiinflammatory drugs are needed. Drug firms continue to develop antiinflammatory drugs often as single enantiomers. As a result the sales of antiinflammatory and analgesics exceeded 223 million US dollars in 2000 and is expected to exceed 241 million US dollar by 2005 (Stinson, 2001).

As far as we are aware, a broad review of the secured patents on plants for antiinflammatory activity is lacking. Further, there are growing apprehensions that the patenting of medicinal plants in the West and in European countries ignores traditional knowledge. However, of 760 medicinal plant patents, under USPTO databases, more than 45% came from traditional claims. The United Nations Industrial Development Organization asserts that systematic investigations and modern technology in the development of plant derived medicines in China, India and Korea has led to a global resurgence in the use of such medicines from all over world the (Velasquez and Boulet, 1999; Darshan and Doreswamy, 1998).

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DATA SOURCES AND ANALYSIS

Patent disseminating services such as Derwent Services, UK, European Patent Office Records, and WIPO database were scrutinized, besides Chemical Abstracts and Medicinal and Aromatic Plants Abstracts database. Standard data sources such as the National formulary of Ayurvedic Medicine (1978) and the National Formulary of Unani Medicine (1981), Government of India Publications; Wealth of India, an Encyclopaedia of Indian Raw Materials & Industrial Products (11 volumes, 1948 onwards) and Plants for a future database 1997–2002 (website: www.uk.leeds.ac.ukpfas/) were referred to for botanical and traditional information The comparative results are given in tabular form and in the text. Patents secured on lower plants such as ferns, fungi, liverworts are not included in this study.

Comprehensive and up-to-date information on the chemistry and pharmacology of 38 plants secured in 50 patents is presented. Current interest in the various areas of inflammation has led to development studies of many remedies linked to traditional medicine. Also, an in depth analogy of these plants used in traditional system/medicine, has been prepared. Some 685 plants species are available for the treatment of various inflammations, divided as follows, antirheumatic 236, analgesic 234, antiinflammatory plants 183, antihaemorrhoidal 19 and antiarthritic 13 (plants for a future database).

The search for new antiinflammatory agents from natural product sources continues to emphasize mechanism based approaches, involving discrete based cellular and biochemical targets. Some of the bioactive compounds, which fall under this category, include alkaloids, flavonoids, tannins, triterpenes, polysaccharides, carbohydrates, volatile oils, lipopolysaccharides and polyunsaturated fatty acids (Table 1). These compounds,

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Table 1. Traditional medicinal plants versus antiinflammatory patented plants

Traditional information	Patent information
1. *Alkanna tinctoria* L. syn *A. tuberculata, Anchusa tinctoria*, Boraginaceae **Eng**: Alkanet Perennial, found throughout S. Europe to Persia in uncultivated lands, calcareous soils and pine forests **Part**: Roots **Traditional use**: Known since ancient times as dyeing agents (alkanet), in the treatment of varicose veins, ulcers, bedsores, itching and rashes etc. **Actions**: Antibacterial, antipruritic astringent and vulnerary **Constituents**: Alkanins	**Patent**: FR 277,872, 1981 Hair colouring components from plant extract exhibit antibacterial and antiinflammatory activity (Phillippe and Rene, 1981)
2. *Azadirachta indica* syn *Melia azadirachta*, Meliaceae **Eng**: Margosa, Neem Large evergreen indigenous tree, found throughout India, originated from the dry zones of the south and South-eastern of Asia, introduced to all Caribbean, specially in Haiti, Dominican Republic and in America Center, with very extensive plantations in Nicaragua **Part**: All parts of plant **Traditional use**: Externally in skin diseases, dandruff, wound healing, internally for liver disorders, jaundice. Blood purifier. Also, to repel insect and pests **Actions**: Antidiabetic, antimalarial (bark), antiinfective, antimicrobial, astringent, and skin problems **Constituents**: Nimbin, nimbinin, nimbidin, beta-sitosterol (Chopra *et al*., 1956, Satyavati *et al*., 1976)	**Patent**: (i) US 5 5,730,986, 1998 (IICT, India) Yield a bioactive extract through solvent extraction and HPLC, exhibiting antiulcer (gastroduodenal ulcer) activity *in vivo* and *in vitro* experimental models (Bandyopadyay, 1998) (ii) JP 58,225,201, 1983 Patented antiinflammatory polysaccharide (Terumo Corporation, 1983)
3. *Berberis vulgaris*, Berberidaceae **Eng**: Barberry A small shrub, native to China, naturalized in temperate regions the world over **Part**: Rhizomes, roots **Traditional use**: As a cathartic (laxative), to increase appetite, as a tonic, to ease heart burn, as a cure for ulcers, upset stomach, and to lower blood pressure **Action**: Root bark bitter tonic, astringent, diuretic **Constituents**: Alklaloids, berberine and oxyacanthine (Chopra *et al*., 1956)	**Patent**: (i) JP 7,862,817, 1979 Antiinflammatory and antiulcer compound berberine has been patented (Terukai and Michinori, 1978) (ii) RO 66,426, 1978 Extraction of alkaloid berberine hydrochloride in pure form has been claimed (Theodor *et al*., 1978) (iii) Indian, IN, 139,204, 1976 Cold process for production of berberine from roots (Dutta *et al*., 1976)
4. Brewer's grain extract Around 25% of the barley crop is used for malting, for which it is steeped in aerated water and germinated. During germination root sprouts emerge, but not the stems. This 'green' malt is used for making beer by fermentation during which hops (*Humulus lupulus*) is added for flavour (and yeast to ferment the sugars into alcohol and carbon dioxide. The hops residue and proteins are then separated from the product, beer (Ambasta, 1986)	**Patent**: Eur. Pat. Appl. 287, 003, 1989 Pharmaceuticals for skin diseases treatment, recovered from Brewer's grain extract. The extract inhibits histamine or nicotine acid induced erythema. A skin ointment contains propylene glycol distearate and made up to 100% by weight. Extract relieved itching of the skin and reported to exhibit antiinflammatory and antimitotic effects (Lother and Hagen, 1989)
5. Bromeliaceae Plants from Bromeliaceae family (names of the plant not mentioned) Some plants of this family, e.g. *Ananas comosus*, *Bromelia* sp contain a protein-digesting enzyme bromelain (bromelin) used to relieve inflammation (Ambasta, 1986)	**Patent**: (i) EP 89,532, 1983 Polysaccharide from raw juices of plants or bromelain extract, which is non-toxic and devoid mutagenic activity. Antiinflammatory activity of the compounds were high with an ED_{50} < 0.3125 pg/kg (intragastric) in the ascite liquid inhibition test in rats (Massimiliano, 1983) (ii) FR 6,400, 1968 Therapeutic compositions consisting of lysozymes and bromelains (obtained from pineapple) with neomycin and or a cortisone derivative, described as antiinflammatory, analgesic, antiinfectious and homeostatic agents (Antoinette and Jean, 1968)
6. *Ceanothus thyrisiflorus*, syn *C. bicolor, C. elegans*, Rhamnaceae **Eng**: California lilac, Blue brush, Blue Blossom evergreen shrub, native of Oregon to California prostrate, evergreen, shrub found on woody slopes, canyon below 600 m **Part**: Bark, root, leaves	**Patent**: US 4,4999, 086, 1985 Leaves and buds on extraction with boiled water at 180 °C and the product obtained after cooling has been tested for poison oak irritation. Exhibit effective antiinflammatory activity against poison oak irritation and inflammation (Frederick, 1985)

Table 1. (*continued*)

Traditional information	Patent information
Traditional use: American tribes and the colonists made teas from the roots (and sometimes the bark) for dysentery, asthma, sore throats, bronchitis, use as a sedative and blood tonic (there being alkaloids in the roots that are mildly hypotensive) and for people under stress. The teas were also highly thought of as a lymphatic remedy, particularly for enlarged lymph nodes and sinus and tonsil inflammations. The colonists sometimes used these teas for menstrual haemorrhaging, nosebleeds and bleeding piles. Some of the local tribes add extract from the flowers to their hair shampoos or use as a rinse **Actions**: Antiinflammatory, antistress, roots antisiphilitic **Constituents**: Alkaloids, saponins (Baig *et al*., 1993)	
7. Chamomilla flos (flowers of *Matricaria chamomilla* syn *M. recutita*, *Chamomilla recutita*), Compositae **Eng**: Chamomile An annual herb, native of Europe, Spain, France and England. Distributed all over the world and the Arctic regions, oldest plant used by Egyptians as an offering to their gods. Because of its apple like smell Greeks called it 'Kamai melon' (ground apple). Its tea, poultice, and oil are used in folk remedies. Indicated in insomnia, vertigo, gastritis, bronchitis, laryngitis **Part**: Flower **Traditional use**: Herbal teas, poultice, spasmodic **Actions**: analgesic, anxiolytic, antioxidant, antispasmodic, antiphlogistic, sedative, hypnotic, antiviral **Constituents**: Flavonoids, sesquiterpenoids (chamazulone) (Tyler, 1994)	**Patent**: (i) BR 800, 819, 1981 Antiinflammatory drug from flower extracts (Otto, 1981) (ii) EP, 89,529, 1983 Fresh flowers extracted with water and homogenized, active compound was precipitated with alcohol or dimethylsulphoxide to yield a polysaccharide concentrate having nitrogen and phosphorus content of approximately 5% and total sugar content of approximately 60% for use as inflammation inhibitor. Antiinflammatory activity against carrageenan-induced oedema was comparable to that of phenylbutazone and indomethacin (Kalman *et al*., 1983)
8. *Cheldonium majus*, Papaveraceae **Eng**: Celandine Perennial or biennial, originated in Eurasia, and native to North Asia, found as a weed in gardens or naturalized in mountains **Part**: Root **Traditional use**: Remedy for cataract, jaundice and liver ailments, used for eye and skin disorders **Actions**: Analgesic, antiinflammatory antihepatotoxic **Constitutents**: Isoquinoline, alkaloids, berberine, cheldonine (Elie, 1988)	**Patent**: PL 139, 290, 1987 Powdered roots extracted with organic acids such as tartaric, citric and oxalic acid and alcohol and buffered at 30°–60 °C. Acid extract is then subjected to CCD techniques with $CHCl_3$ and vacuum evaporation. Residue is dissolved in hot methanol, crystallized and purified. Protopine recovered, is analgesic and has curare like activities and has characteristics similar to morphine (Leon *et al*., 1987)
9. *Chrysantellum americanum* syn *C. indicum*, Asteraceae **Eng**: Crisantello Prostrate or decumbent, much branched annual; originated in America and introduced into Europe and India **Part**: Whole plant/leaves/flowers/root **Traditional use**: In pancreas and liver disorders, gallstones, urinary and renal calculations, circulatory problems, arthritis, its cream and gel used for massage, bruised leaves in headache, roots in toothache **Actions**: Eliminate gallstones, hepatoprotective, antiinflammatory, venotonic, antipedematous, hyperlipidaemic, hypocholesterolaemic **Constituents**: Chrysantellins, flavonoids, saponosides (Chopra *et al*., 1956)	**Patent**: DE 2,801,186, 1978 Leaves yield a rich triterpenic compound and saponin derivatives of echinocystic acid, useful in human and veterinary medicine, and exhibit antiinflammatory, analgesic and capillary protective activities (Henri *et al*., 1978)
10. *Coleus forskohlii syn C. barbatus*, Lamiaceae **Eng**: Makandi Perennial, originated in India, grow wild on mountain slopes of India, Nepal, Thailand **Part**: Roots **Traditional use**: As recorded in ancient Sanskrit texts it was used to treat heart and lung diseases, insomnia **Actions**: Antiasthmatic, to treat glaucoma **Constituents**: Diterpenes, forskholin (Ambasta, 1986; Satyavati *et al*., 1976)	**Patent**: EP 448,029, 1991 Forskolin derivatives Ri $(CO\text{-}CH_2)_n$ N (R4) R3 where R_3 = R4 = H lower alkyl or together are low alkylene with possible O or N in linking chains R2 = C_{2-3} hydrocarbon n = 1–5 Forskolin derivatives are used to inhibit skin ulcers (Makoto *et al*., 1991)

Table 1. (*continued*)

Traditional information	Patent information
11. *Curcuma domestica*, syn *C. longa*, or *C. xanthorrhiza*, Zingiberaceae **Eng**: Turmeric **Part**: Rhizome Originated in Southeast Asia or South Asia. In Indonesia fresh leaves are used as flavouring. A related species *C. xanthorrhiza*, grown in Java, called Tamu lawak, in Europe called Indian saffron **Traditional use**: Wound dressing, respiratory diseases such as cough cold, indigestion, dyspepsia, jaundice and liver disorders, skin problems, fevers, flatulence and constipation **Actions**: Antihepatotoxic, antimicrobial, antitumour, antifrost, antiburn **Constituents**: Curcuminoids, curcumin (Arora *et al.*, 1971; Tyler, 1994)	**Patent**: (i) EP 440, 885, 1991 Process of extraction of bis-dismethoxy curcumin from curcuminoids of *C. domestica* or *C. xanthorrhiza* rhizomes, dried and soaked in petroleum ether, residue treated with ethanol to get curcuminoids. Addition of essential oil enhanced antiinflammatory activity. Curcuminoids showed antiinflammatory activity by inhibiting carrageenan induced oedema in rats by 28.6% (Liang, 1991) (ii) US 5,120,538, 1992 Combination of compounds isolated from *Curcuma* sp. as antiinflammatory (Oci, 1992)
12. *Eucalyptus globules*, Myrtaceae **Eng**: Tasmanian Blue-Gum Tall tree found from Australia to Tasmania, Victoria, in damp marshland in deep rich soil, cultivated in warm climates, introduced into India **Part**: Leaves/flowers **Traditional use**: Essential oil from leaves as an antiseptic, to relieve cough, cold, sore throats, deodorant, febrifuge, rheumatism, burns **Actions**: Antispasmodic, stimulant, expectorant, antibacterial, astringent (oleoresin), antiinflammatory **Constituents**: Sesquiterpenes, alcohols, cineol (Parrota, 2001; Tyler, 1994)	**Patent**: (i) JP 81,20, 590, 1981 Physiologically active substances, EK and EA from dry buds (names not disclosed), shown to be antiinflammatory (Takeda, 1981) (ii) FR 248,949, 1980 Dermatological compositions based on eucalyptus oil (William, 1980)
13. *Euphrasia* sp., Scrophulariaceae Most commonly used species of *Euphrasia* is *E. officinalis* **Eng**: Eyebright Semiparasitic annual herb, native to Britain, the European continent, subarctic regions of N. America **Part**: Aerial parts **Traditional use**: Extract of leaves used as eyewash since the Middle Ages that is why the name 'eyebright', in hay fever, catarrh, in inflammation of eyes, mouth and throat; as a lotion for conjunctivitis. In E. Europe used internally and externally to treat blepharitis and conjunctivitis and poultice for styes and eye fatigue **Actions**: Anticonjunctivitis, antibacterial, antiinflammatory **Constituents**: Glycosides (acubin), saponins, tannins, resin, phenol carboxylic acid (Chopra *et al.*, 1956; Ambasta, 1986)	**Patent**: US, 5,204, 105, 1993 Emulsified composition (comprising extracts from different plants (butcher broom, hydrocotyl, horse chestnut, calendula, hamamelis, horsetail, peach, lady's mantle, ivy, chamomila, comfrey, and yeast) for treatment of the skin under the eye and to reduce puffiness, irritation and inflammation of the skin under the eyes (Mausner, 1993)
14. *Gentiana scabra and G. macrophylla*, Gentianaceae **Eng**: Gentian, Oin Jiao (Chinese) *G. scabra* – perennial, native of Japan *G. macrophylla* – perennial found in East Asia, China, Siberia (Both have similar uses and properties) **Part**: Root, leaves **Traditional use**: Oin Jiao has been used in Chinese herbalism for over 2000 years as an excellent tonic for digestive system, work on stomach, liver and gall bladder **Actions**: Analgesic, antipyretic, antirheumatic, diuretic antihepatotoxic **Constituents**: Secoirridoids *Swertia japonia*, Gentianaceae Annual, occurs in East Asia-Japan **Part**: Leaves **Traditional use**: Treatment of digestive disorders **Actions**: Antihepatotoxic, stomachic, bitter tonic **Constituents**: Gentiopicroside (Frost and Tyler, 2000)	**Patent**: JP 79, 26, 323, 1977 A mixture of secoiridoids from *Gentiana* sp and gentiopicroside from *Swertia japonica* exhibit antiinflammatory activity (Terukai *et al.*, 1978)
15. *Glycine max* syn *G. soja, G. hispida, Soja max*, Leguminosae **Eng**: Soyabean Annual climber, found in East Asia especially in lowland thickets of C. and S. Japan, used in Asia, China, Africa	**Patent**: German GE 2, 911, 353, 1979 Soya saponins on hydrolysis yield 3-0-beta-glucopyranosyl, soya sapogenol-B or obtained from *Stachybotrys* cultures. Pharmaceutical compositions are useful for rheumatic diseases, nephritis or autoimmune disease (Masanao *et al.*, 1979)

Table 1. (*continued*)

Traditional information	Patent information
Part: Seeds, leaves, bark **Traditional use**: Fermented seeds are diaphoretics and stomachic, to treat colds, fevers, headaches, insomnia, irritability and stuffy sensation in the chest, seed sprouts are laxative and used to cure oedema, dysuria, bruised leaves applied to snakebite, bark decoction is astringent **Actions**: Antidote, astringent, diaphoretic, laxative, stomachic, resolvent, oestrogenic **Constituents**: Saponins, flavonoids, isoflavonoids (Satyavati *et al*., 1976; Ambasta, 1986)	
16. *Glycyrrhiza* L., Leguminosae **Eng**: Licorice *Glycyrrhiza glabra* European licorice and *G. uralensis*, Chinese licorice Perennial herb, native to Europe, Asia, North and South America as well as Australia. It is extensively cultivated in Russia, Spain, Iran and India. It is one of the most popular and widely consumed herbs in the world. The English name licorice is derived from '*liquiritia*', itself a corruption of the ancient name *Glycyrrhiza*, which now serves as the scientific generic name. European plantings of the herb were established almost a thousand years ago. The first century Roman naturalist Pliny mentions that licorice is native to Sicily. Theophrastus noted the sweet flavour of the roots and says it is used for asthma, dry cough, and all diseases of the lungs. In the American market the Chinese commercial licorice root is cheaper than its European counterpart **Part**: Root in the making of powder, teas and tonics, extracts, tinctures and decoctions **Traditional use**: Expectorant, demulcent, moderately pectoral and emollient. It is a popular and well-known remedy for coughs, consumption and chest complaints generally most notably bronchitis, and is an ingredients in almost all popular cough medicines on account of its valuable soothing properties **Actions**: Antiallergenic antibacterial, antiinflammatory, antipyretic, antioxidant, antispasmodic, antiviral, immunomodulatory, antitussive, anticancer **Constituents**: Glycyrrhizic acid, a triterpenoid saponin; flavonoids and isoflavonoids (Frost and Tyler, 2000; Fluck *et al*., 1976)	**Patent**: *Glycyrrhiza glabra* (i) JP 58,49 310, 1983 Glycyrrhetin solution prepared from the root. Its solubility increased on treatment with urea or sodium benzoate. Exhibit antiinflammatory activity (Minophagen Pharmaceuticals, 1983) (ii) USSR, SU. 189,453, 1984 Concentrated solution of licorice extract yielded glycyrrham, a triammonium salt of glycyrrhizic acid, on separation and crystallography (Manyak and Muravev, 1984) (iii) JP, 7,005,022, 1977 Analgesic, antipyretic, antitussive and stable pharmaceuticals, from licorice extracts (Muneaki and Kenzo, 1977) (iv) USSR, SU 1,499,902, 1991 Glycyrrhizic acid triamides exhibit antiinflammatory activity (Ballina *et al*., 1991) *Glycyrrhiza uralensis* (i) JP. 02, 150, 290, 1990 Glycyrrhiza roots infected with *Agrobacterium* yield glycyrrhizin, which on treatment with urea solution or sodium benzoate exhibits, antiinflammatory activity. To get roots infected with *Agrobacterium*, seeds of *Glycyrrhiza* were cultured in agar medium infected with *A. rhizogenes* ATCC 158034 and propagated as calform free medium. Hairy roots contained 1.18%–2.98% wt. glycyrrhizin useful as antiinflammatory agent (Ushio, 1990) (ii) JP 78, 62,817, 1978 Yield antiulcer and antiinflammatory glycyrrhizinate (Terukai *et al*., 1978) (iii) JP 81,51,500, 1981 Glycyrrhizin from licorice (Maruzen Chemical Company, 1981)
17. *Gynostemma pentaphyllum*, Cucurbitaceae **Eng**: Sweet tea vine Annual/perennial found in East Asia, China, Japan, Korea, Indonesia, Malaysia thickets of low land (all over Japan) mostly in cultivated beds **Part**: Whole plant **Traditional use**: Tonic (in a conference in Beijing in 1919, rated among 10 best tonic herbs), leaves as tea (known as Brain tea and awarded numerous medals in China) herbs improves circulation, liver functions, strengthens immune and nervous system, reduces blood sugar and cholesterol levels, relieves spasms **Actions**: Antihepatotoxic, immunostimulatory and antispasmodic **Constituents**: Saponins	**Patent**: JP 5,857, 398, 1983 Aerial parts yield saponin, named gypenoside, which exhibit antiulcer activity (Takemato, 1983)
18. *Hamamelis virginiana*, Hamamelidaceae **Eng**: Witch hazel Deciduous shrub or small tree, indigenous to Eastern America (Virgnia) and Southern Canada. Origin of name is from Greek, Hamatus meaning '*hooked*' and melon means 'apple' because of appearance of fruit, a nut with hook like appendages **Part**: Leaves, bark	**Patent**: RO 64, 207, 1978 A venotropic ointment active against varicose veins, haemorrhoids was prepared by mixing rutin, lanolin and extracts of both the plants (Emanoil *et al*., 1978)

Table 1. (*continued*)

Traditional information	Patent information
Traditional use: Witch hazel as the name suggests forked branches were used as divining rod while searching for water and ores. Used in haemorrhages, congestion, inflammation of eyes and skin burns, haemorrhoids **Actions**: Antiinflammatory, antidysenteric, antidiarroheal, antihaemorrhagic, astringent **Constituents**: Catechins, proanthocyanidins, flavanoids, volatile oil (Zeylstra, 1998) *Aesculus hippocastanum*, Hippocastanaceae **Eng**: Horse chestnut Large deciduous tree, native of Albania, Greece and Bulgaria, introduced and widely cultivated in India, Europe and Russia **Part**: Leaves, seeds **Traditional use**: Bleeding piles, varicose veins, venous stasis, thrombosis, whooping cough, inflammatory oedema. In European folk medicine, carrying fruits in pockets was believed to prevent or cure arthritis, in Germany used for the management of chronic venous insufficiency **Actions**: Strengthen blood vessels, antithrombotic, antihaemorrohoidic, astringent, haemolytic **Constituents**: Saponin, aescine, flavones, coumarins, tannins (Tiffany *et al*., 2002)	
19. *Harpagophytum procumbens*, Pedaliaceae **Eng**: Devils claw/Car apple African plant, perennial, named Devil's claw because of its peculiar fruits covered with grappling hooks **Part**: Dried tubers, roots/rhizome **Traditional use**: Gout, arthritis, in diabetes treatment, in Africa for muscular pain and gout **Actions**: Analgesic, antiinflammatory **Constituents**: iridoids, glycosides, harpagoside and procumbide (Frost and Tyler, 2000)	**Patent**: FR 2,614, 791, 1988. Plant extract containing 4% harpagoside admixed with selenium or zinc along with yeast as support materials yield a product, which is useful in the antiinflammatory analgesic and antirheumatism treatment (Elie, 1988)
20. *Hedera helix*, Araliacae **Eng**: English ivy, Nepal ivy, Root climber, found in Canary island, W and C. Europe, USA, W. Himalayas to Korea **Part**: Leaves, berries, wood **Traditional use**: Berries purgative, useful in febrile diseases, dry leaves used to stimulate sores **Actions**: Expectorant, diaphoretic, cathartic, haemolytic Adverse effects on heart reported. **Constituent**: Saponins, (hederagenin, hederin), glycoside (helexin) (Chopra *et al*., 1956)	**Patent**: (i) Fr. M, 6,218, 1968 Non-toxic sapogenin-triterpene complexes from the extract of ivy wood exhibit antitussive, spasmolytic and antiinflammtory activity (Pierre, 1968) (ii) Fr. 2, 459, 048, 1981 Leaves extract preparation and isolation of constituents (Jean and Marcel, 1981)
21. *Humulus lupulus*, Moraceae **Eng**: Hops Perennial climber, Native of N. America and N. Asia **Part**: Fruits, herb **Traditional use**: Fruits (strobilus) used in insomnia, nervous conditions, herb infusion considered as sedative **Actions**: Appetite stimulatory, antibiotic, sedative, regularize menstrual cycle **Constituents**: Lupamaric acid or bitter principle (Chopra *et al*., 1956; Fluck *et al*., 1976)	**Patent**: Neth. NL, 8,203,249, 1983 Combination of herbs claimed to exhibit curative action against arthritic rheumatic diseases. Also, addition of small amounts of *diazem* tablets cause synergistic effect on the action of various herbal preparations (Johannes and Marie, 1984)
22. *Luffa cyclindrica* syn *L. aegyptiaca*, Cucurbitaceae **Eng**: Sponge gourd, luffa, sponge luffa, bath sponge. Annual climbing/running vine, found mainly in China, Korea, India, Japan and Central America **Part**: Fruits/leaves/seeds **Traditional use**: In India fresh fruits used as vegetable, fruit skeleton as bath sponge, seeds as laxative and tonic. In Suriname traditional medicine tea of leaves used as diuretic, while juice of fruit against internal haemorrhage. New Zealand import *Luffa* for bathroom uses **Actions**: Laxative, diuretic, antihaemorrhagic, homeostatic **Constituents**: Saponin glycosides (Ambasta, 1986)	**Patent**: (i) JP, 04, 36,215, 1992 Fluid from plant along with glycyrrhetinic acid and its salt allantoin, salicylic acid and bisabolol yield, cosmetic ointment that exhibit antiinflammatory activity on skin and used in sunburn (Mitsuaki *et al*., 1992) (ii) JP 58,105,924, 1983 Defatted seeds yield protein inhibitors (Teijin Ltd., 1983) (iii) JP 63, 179, 819, 1988 Extraction of ginsenoside and lucyoside for the treatment of skin around the anus in patients with haemorrhoids (Ichirio and Michio, 1988)

Table 1. (*continued*)

Traditional information	Patent information
23. *Panex ginseng* syn *P. schinsenga*, Araliaceae **Eng**: Ginseng, Chinese ginseng, Orient ginseng Scattered from East Asia-China, Korea in mountainous forests woodland and deep shade **Part**: Root/rhizome/leaf **Traditional use**: Root tea as an adaptogen, used as an emetic and expectorant. It is used as a herbal medicine in the orient for last 5000 and is life prolonging. Also used in Britain, France, Russia, US, Japan **Actions**: Adaptogen, expectorant, nervine tonic, radioprotective *P. quinquefolium* syn. *P. quinquefolius*, Araliaceae **Eng**: American ginseng Found in E. Asia, N. Eastern America, Maine to Georgia, West to Oklahoma and Prinnesota, mostly in rich cool woods **Part**: Roots/leaves **Traditional use**: Tea made from roots and leaves, dried root as masticatory **Actions**: Similar to *P. ginseng* but milder *P. japonicus* syn *P. pseudoginseng* **Eng**: Japanese ginseng Found in Asia to China, Japan **Part**: Root **Traditional use**: Root decoction as an expectorant, febrifuge, stomachic **Action**: Expectorant, antipyretic, tonic (Tyler, 1994; Frost and Tyler, 2000) All above species are perennials and have saponins as main components	**Patent**: (i) JP 79, 135, 210, 1979 Therapeutic agent for ulcer (Shigaru *et al.*, 1979) (ii) CN 1, 057, 267, 1991 Process described for the manufacture of ginseng polypeptide and saponin (Jin and Wenyuan, 1991)
24. *Pinus sylvestris*, Pinaceae **Eng**: Scotch Pine, Scots Pine, Irish Giuis Tall evergreen tree native to Britain, distributed all over Scotland, Europe and Asia, cultivated in Austria, the countries of Scandinavia and United States **Traditional use**: Pine oil in respiratory diseases (steam inhalation) to repel parasite and insect, bactericidal, urinary tract infections, arthritis, rheumatism, gout, needle was used by ancient Romans and Greeks to treat respiratory problems and muscular pains **Actions**: Restorative, stimulant, insecticidal, vermifuge, disinfectant, antiviral, antiarthritic, antirheumatic **Constituents**: Pinenes, careen (Fluck *et al.*, 1976)	**Patent**: JP 04, 49, 241, 1992 Contain lipopolysaccharides isolated from pine, wheat, rice and seaweeds (Genichiro *et al.*, 1992)
25. *Plantago lanceolata*, Plantaginaceae **Eng**: Long plantain, Snake plantain Perennial, native to Central Europe, wide spread in Britain, Eastern Europe **Part**: Seeds, dried leaves **Traditional use**: Leaf infusion in persistent bronchitis, imbibed seeds as mild purgative in diarrhoea, as a poultice, decoction as gargle, eye wash in blepharitis and conjunctivitis **Actions**: Bacterostatic, epithelization, diuretic, purgative, antidiarrhoeal **Constituents**: Pentacyclic triterpenes, oleanolic acid, mucilage, glycoside aucubin (Satyavati *et al.*, 1976; Ambasta, 1986)	**Patent**: Rom. RO 60,244, 1983 Antiseptic and antiinflammatory compound contain dilute alcohol extract of plant 20–40% and acetyl pyridium bromide (Constania *et al.*, 1983)
26. *Prunus persica* syn *P. vulgaris, Amygdalus persica, A. communis*, Rosaceae **Eng**: Peach Deciduous tree, found in East Asia to China, in woodland, sunny edge, draped shade **Part**: Fruits, leaves, flowers, stems, seeds **Traditional Use**: Fruits stomachic, demulcent, considered useful as ascaricide (Fluck *et al.*, 1976). Leaves astringent, demulcent, diuretic, febrifuge, laxative, parasiticidal, and mildly sedative, and vermifuge, used	**Patent**: JP 58, 172,321, 1983 Water extracts of seeds yield analgesic and antiinflammatory high molecular weight proteins (Dainippon Pharmaceuticals, 1983)

Table 1. (*continued*)

Traditional information	Patent information
internally in the treatment of constipation and oedema. Seeds used in constipation **Actions**: Gum from stems is alterative, astringent, demulcent and sedative, expectorant (Chopra *et al*., 1956) **Constituents**: Hydrocyanic acid	
27. *Rabdosia rubescens*, Lamiaceae **Eng**: Rabdosia Chinese herb **Part**: Leaves, whole herb **Traditional use**: Clear away heat and toxic material, nourish yin, remove blood stasis and relieve swelling, or carcinoma of oesophagus, breast and liver, especially effective for epithelial hyperplasia of oesophagus, in sore throat, cough, mammary abscess, trauma **Actions**: Antitumour, anticarcinogenic, cure oesophagism **Constituents**: Rubescensins A and B, terpenes, flavones, organic acids	**Patent**: JP 57, 179, 185, 1982 Antitumour and antiinflammatory compound rubescensin C has been extracted from leaves by refluxing with methanol (Taiho Pharmaceuticals, 1982)
28. Raisins (dried fruits of *Vitis vinifera*, Vitaceae) **Eng**: Grapes, wine grapes Large deciduous climber, climbing by means of tendrils **Part**: Dried fruits **Traditional use**: Capillary bleeding in diabetes, oedema and inflammation from injury **Actions**: Laxative, stomachic, diuretic, demulcent, and cooling, astringent in throat infections, health tonic **Constituents**: Bioflavonoids, catechins, anthocyanogenic tannins (Satyavati *et al*., 1976; Tyler, 1994)	**Patent**: PL. 147, 908, 1989 Raisins on extraction with ethanol at room temperature yield extract containing vitamin K, E and D and flavonoids, anthocyanins, phenols, polyacetalenes, resins, balsams and essential oils Extracts were formulated in ointment to treat ache (Roman *et al*., 1998)
29. *Rosmarinus officianalis*, Lamiaceae **Eng**: Rosemary Evergreen shrub, found from S. Europe to W. Asia, in cultivated beds, woodland, hedge, used in Mexico, Panama, Peru, Sicily, Spain, Turkey, Venezuela, India **Part**: Whole plant, leaves, stem, flowers **Traditional use**: Infusion of stems and flowers for treating headaches, cold, colic, distilled water from flowers used as an eyewash, essential oil used as rubefacient, tonic **Actions**: Antiseptic, antispasmodic, astringent, antioxidant antidepressant, carminative cholagogue, diaphoretic, nervine **Constituents**: Rosemarinic acid, flavonoids (Fluck *et al*., 1976; Frost and Tyler, 2000)	**Patent**: (i) DE 295, 214, 1981 Mixture of plant ingredients in the form of tincture of capsicum, rosemary oil, and camphor compounds as an ointment for the treatment of accidental sport related muscloskeletal trauma (Meinhard *et al*., 1981) (ii) Ger Offen DE 3,009, 143, 1981 Extract of plant useful as an antiinflammatory (Hans, 1980)
30. *Sanguisorba officinalis*, Rosaceae **Eng**: Garden Burnet, Common Burnet Perennial herb (rhizomatous), native to California, mostly found in California, but is confined to western North America, widespread in the northern temperate regions of Europe, Asia, and North America, grows in moist meadows and shady places, chiefly in mountainous districts, almost all over Europe, common in Britain, but rare in Ireland **Part**: Herb, root, whole plant **Traditional use**: As a vulnerary, hence its generic name, from sanguis (blood) and sorbeo (to staunch), herb and root administered internally in all abnormal discharges, in female disorders, peptic ulcer, haematuria, menorrhagia, dysentery. In addition to its medicinal applications, it is used as a vegetable and added to salads **Actions**: Astringent, a tonic cordial and sudorific, haemostatic, antibacterial, antiemetic, promotes healing of burns, stop ulcer bleeding, refrigerant to blood **Constituents**: Sanguisorbin, tannins, triterpenoids (Ishimaru *et al*., 1990; Reher and Budesinsky, 1992). For use plant extracts are mixed with Chinese and Indian plants such as, *Phellodendron, Scutellaria baicalensis, Rheum palmatum, Lithospermum euchromum, Punica granatum*, Chinese *Angelica, Rehmannia glutinosa, Boswellia carterri, Commiphora myrrha*	**Patent**: CN. 1,032,249, 1982 (i) Extracts of root bark, bulbs and peels admixed with gel prepared from chitosamine and pulverized pig skin along with tortoise plastron, borneol and K.Al (SO4) 2 promote skin healing, useful as artificial skin and exhibits antiinflammatory activity (Baocheng *et al*., 1989) (ii) JP 5,838,209, 1983 Antiinflammatory preparation containing tannins for skins (Sunstar Incorporation, 1983)

Table 1. (*continued*)

Traditional information	Patent information
31. *Scutellaria baicalensis* syn *S. macrontha*, Lamiaceae **Eng**: Baikal skullcap Perennial, found in S. Africa, East Asia, China, Japan, in sandy and rocky places along seashore, grassy slopes **Part**: Leaves, roots, seeds/whole plant **Traditional use**: In Chinese herbalism leaves tea used to treat dysentery and diarrhoea and is considered to be one of the 50 fundamental herbs, also used in jaundice, haemorrhage, seed used to cleanse bowels of blood and pus **Actions**: Antibacterial, anodyne, antipyretic, sedative, antispasmodic, nervine, antiallergic **Constituents**: Flavonoids (Tyler, 1994; Frost and Tyler, 2000)	**Patent**: JP 80, 127, 309, 1980 Plant extract is antiinflammatory, besides use for skin burns, used in skin preparations (Kishohin, 1980)
32. *Stephania* sp., Menispermaceae Roots of *S. japonica* used for fever, diarrhoea, dyspepsia and urinary diseases, septic inflammations, in Cochin (India) roots and in China roots and tubers of *S. glabra* used in pulmonary tuberculosis, asthma, fevers, dysentery (Chopra *et al*., 1956). *Stephania* mixed with 12 other plants such as *Coix* sp (Gramineae, roots for diseases of air passage and urinary tract), *Pinellia* sp (Araceae), *Prunus* sp (Rosaceae, in S. E. & C. Africa root and bark used for inflammation of prostate gland and kidney diseases), *Phellodendron* sp (Rutaceae, bark in skin disorders), *Sophora* sp (Leguminosae, root decoction applied in headache, juice in eye sore), *Tetrapanax* sp (Araliaceae), *Stemona* sp (Stemonaceae), *Glycyrrhiza* sp (Leguminosae, roots in genitourinary diseases, sore throat), *Tripterygium* sp (Celastraceae), *Forsythia* sp (Oleaceae), *Siegesbeckia* sp (Asteraceae, useful in healing gangrenous ulcers and sores and in diseases of skin and urethra) (Moore, 1998; Hou, 1999)	**Patent**: US 5,908, 628, 1999 Composition of 12 plants, talc and silkworm excrement have analgesic, antipyretic and antiinflammatory activities. Methods of using such composition for treating such diseases, including osteoarthritis and rheumatoid arthritis also provided (Hou, 1999)
33. *Tabernaemontana orientalis* syn *Ervatamia orientalis E. pubescens, E. angustifolia*, Apocynaceae **Eng**: Iodine bush, Bitter bark Evergreen shrub to small tree, distributed in Indonesia, New Guinea, N. Australia and Pacific region, found in monsoon forest thickets, sand dunes. It is closely related to *T. divaricata*, a plant indigenous to India **Part**: Leaves, bark especially root bark **Traditional use**: Latex used by aborigines to cure sores and ulcers, have wound healing (antibiotic) property, hence named as Iodine bush, also called Bitter bark because of its use as a substitute of quinine in colonial times **Actions**: Analgesic, sedative, local anaesthetic, antifatigue **Constituents**: Alkaloids, dregamine, ervatamine, vabosine, voaconine, ibogain, boacristine	**Patent**: Fr. Demande FR 2,03,7,003, 1969 Bark of the tree yields an alkaloid dregamine, used in antiinflammatory and antiviral medicaments, for the treatment of nervous asthenia, respiratory depressions, and type III poliovirus (Louisette and Odile, 1969)
34. *Tanacetum parthenium* syn *Chrysanthemum parthenium*, Asteraceae **Eng**: Feverfew Annual or perennial **Part**: Leaves **Traditional use**: Headaches, migraines, arthritis, allaying nausea; vomiting, to relieve inflammation, asthma attacks, promote sleep, improves digestion, help in melancholy and heaviness or sadness **Actions**: Anthelmintic, antiinflammatory, antispasmodic, antimigraine, antihistaminic, antidepressant **Constituents**: Sesquiterpene lactones (parthenolide), flavones (Moore, 1998)	**Patent**: US 6,274,176, 2001 Edible composition containing at least three from the group of seven herbs, the preferred composition contains: *Tanacetum parthenium*, *Curcuma longa* and *Zingiber officinale* in equal amounts for alleviation of arthritis and gout (Tomer, 2001)
35. *Uncaria gambir*, Naucleaceae **Eng**: Gambier Climbing shrub (by hooks) becomes woody, native of Malacca, grows in plantations of Singapore and neighbouring islands	**Patent**: Belgian, BE 886, 568, 1988 Leaves yield phenolic compound, catechin used for the treatment of degenerative diseases such as joint cartilage (Georges *et al*., 1988)

Table 1. (*continued*)

Traditional information	Patent information
Part: Leaves **Traditional use**: Source of Gambier or Pale Catechu used largely for tanning, as masticatory, headaches, spasms **Actions**: Antiinflammatory, antihypertensive, astringent **Constituents**: Alkaloids, gambridine, isogambridin, catechin, catechutannic acid (Ambasta, 1986)	
36. *Withania somnifera*, Solanaceae **Eng**: Winter cherry, Indian ginseng Erect, evergreen, tomentose shrub, native to India, found throughout drier parts in waste places also cultivated to some extent for the medicinal roots. The Greek physician Theophrastus described it. Also recorded in the Arabib 'Kaknaj-el-manoum', Rheede calls it 'pevetti' and states that a vulnerary ointment was prepared from the leaves in the late 1880s. Dr Trebut investigated its reputation for hypnotic properties. R. L. Simmoneds (*Am J Pharm* Feb., 1891) stated the use of plant at the Civil Hospital Alger, as a sedative and hypnotic. In Ayurveda called Aswagandha in Sanskrit, means smelling like a horse or mare. Used in African and Indian system of medicine **Part**: Roots, leaves, fruits, seeds **Traditional use**: Tonic for general weakness, as aphrodisiac, geriatric, rheumatism, asthma, cough, antispasmodic, uterine, sedative, relaxant on intestinal, bronchial, tracheal and blood vascular muscles, used in fever and skin problems such as ringworm **Actions**: Immunostimulatory, memory enhancer, general health tonic **Constituents**: Alkaloids, cuscohygrine, anahygrine, tropine, pseudotropine, anaferine (Chopra *et al*., 1956)	**Patent**: (i) South Africa SA 950, 908, 1995 A synergistic formulation, Arenil and Withalil, derived from *Withania* admixture of the leaves of plants; *Curcuma longa, Inula racemosa, Paedaria foetida* and *Boswellia serrata*, along with ingredients such as chelated zinc, bala (*Sida acuta*), garlic, wild Himalayan cherry. Arenil (3–15.5 g/kg) and Withalil (6–30.37 g/kg) had significant effect in the treatment of rheumatoid arthritis and osteoarthritis, respectively, without any side effects (Joshi, 1995) (ii) US, 5,494,668, 1996 Similar extracts prepared by admixture of *Withania* (Ashwagandha), *Boswelia serrata, Curcuma longa, Zingiber fficinale* and zinc sulphate to treat degenerative musculo-skeletal diseases (Patwardhan, 1996)
37. *Zanthoxylum simulans*, Rutaceae **Eng**: Peppercorn, Chinese pepper, Szechuan peppercorn, Deciduous bush or small tree, native to China, found wild in China and East Asia, Africa, South America, and West Indies **Part**: Seeds/root, berries **Traditional use**: Seeds are bitter and discarded, seed peel or shell as spice **Actions**: Anodyne, anthelmintic, antidote, antiphlogistic, astringent, carminative, diaphoretic, digestive, diuretic, emmenagogue, stimulant, stomachic, tonic, vasodilator **Constituents**: Alkaloids	**Patent**: US, 4, 767, 626, 1988 Root, stem bark and berries on milling followed by extraction with methanol yielded compounds viz., chelerythrin, oxy-chelerythrine, skimmiarine, 8-methoxy-N-methyl-flindersine. Fat-soluble alkaloid from root in combination with brufen is helpful in alleviating the anaemia associated with viral and bacterial infection in patients with rheumatoid arthritis. Also used to treat joint inflammation (Rudolf and Gyorgy, 1988; Theodore, 1988)
38. *Zingiber officinale*, Zingiberaceae **Eng**: Ginger Herbaceous, rhizomatous, perennial, cultivated all over India, native of China as it was known there as early 400BC. The Greeks and Romans used it as a spice, who thought it was of Arabian origin because it was sent from India through Red Sea. Spaniards introduced it into Jamaica and other islands of West Indies, from where it was exported to Spain around the year 547 AD **Part**: Rhizome, root **Traditional use**: In the East used to promote strength and long life, women of Senegal weave ginger root into belts to arouse their husbands, fresh ginger is used in China to treat toothache, diarrhoea, excess mucus, rheumatism and dysentery. In the West used as a digestive aid, the British Pharmacopoeia lists it for motion sickness. It is the best aid for travel or motion sickness **Actions**: Bactericide, antiseptic, antimicrobial, astringent, antispasmodic, antitoxic, antifungal, diuretic, tonic, carminative immunostimulant. Also insecticidal **Constituents**: Zingiberines (alpha and beta), zingiberol (Chopra *et al*., 1956; Mustafa and Srivastava, 1990)	**Patent**: JP, 0, 585,931, 1993 Diterpene from rhizomes inhibit leukotriene and prostaglandin formation at concentration $4{:}0 \times 16^{-6}$ M by inhibiting 50% 5-lipoxygenase and at 1×10^{-4} M cyclooxygenase by 23.6%, thus, exhibits antiinflammatory activity as indomethacin at 0.75×10^{-6} M inhibits cyclooxygenase by 50% (Takashi *et al*., 1993)

with different structure–activity relationships exhibit antiinflammatory response processes in various *in vivo* and *in vitro* inflammatory models. These models include carrageenan-induced oedema, mediated by histamine (5HT). In these cases, the mechanism of action involves alternate receptor systems along with H1 and H2 receptors. In other cases, synthesis and metabolism of kinins, involving phytophysiological factors that trigger kinin formation and how bradykinin influences the eicosanoid pathway and prostaglandin mediate formaldehyde oedema will come into play. The synthesis of prostaglandins, thromboaxanes and leukotrienes during arachidonic acid metabolism also plays a significant role (Banerjee, 2001). Hence, knowing the key enzymes that affect the eicosanoid pathway, vis-a-vis the pharmacological actions of PGE2, PGF2 and PG12 (prostacyclin) and leukotrienes (LTA4 through LTB4) leads to the mechanism of leukotriene antagonists. Mast cell amines, polymononuclear leucocytes and PAF acether mediate zymosan oedema, while prostanoids and leukocytes mediate croton oil induced inflammation. In the European patent claim on barley, pharmaceuticals from Brewers' grain extract inhibit histamine or nicotinic acid induced erythema and an ointment has been reported to exhibit antiinflammatory and antimitotic effects. Active constituents may act on multiple targets in the inflammatory response process and to reverse the tissue function to the normal phase.

Polysaccharides from plants such as *Matricaria chamomilla* have been reported to inhibit an increase in vascular permeability and enhance phagocytosis *in vivo.* A polysaccharide obtained from powdered dry bark of *Melia azadirachta* containing the sugars, glucose, arabinose and a fucose in the proportion of 1:1:1 with a molecular weight equivalent to 8400, has been demonstrated to inhibit inflammation (Terumo Corporation, 1983). The patent claims a polysaccharide compound, which is active at 25 mg/kg, when administered orally against carrageenin-induced inflammation. A similar patent claim from Japan on a lipopolysaccharide from cereals (wheat and rice), pine and seaweeds, which stimulates TNF-alpha and NO (nitric oxide) production during T-cell proliferation, has been well documented. In this claim, cereals are utilized in different combinations with pine and seaweeds (Gheorghe *et al.*, 1981; Ringborn *et al.*, 2001; Seo *et al.*, 2001). Fresh flowers of chamomile yield a polysaccharide with a nitrogen and phosphorus content of approximately 5%, according to a European patent claim; its inhibitory effect was comparable to that of phenyl butazone and indomethacin (Kalman *et al.*, 1983; Otto, 1981; Srivastava and Kulshreshtha, 1989). A Chinese patent on ginseng polysaccharide production has also been produced (Jin and Wenyuan, 1991). The raw juice or bromelain extracts of plants belonging to the family Bromeliaceae claims in a European patent to yield polysaccharide, which is non-toxic and possesses antiinflammatory activity with an ED_{50} less than 0.3125 pg/kg (intragastric) in an ascite liquid inhibition test and is devoid of mutagenic activity (Robak and Gryglewski, 1996).

The Japanese firm, Nippon Tobacco, Sanyo, has patented diterpene compounds for inhibition of leukotriene formation. The active diterpene at a concentration in the range of 4×10^{-6} M has been reported to inhibit lipoxygenase by 50%. Diterpene compounds are also patented for their inhibitory effect on the production of NO and prostaglandins. The compound at 1×10^{-4} M inhibited (23.6%) cyclo-oxygenase. Among the inflammatory mediators released from activated macrophages, NO and prostaglandin E2 (PGE2) are critical mediators produced at inflammatory sites by two inducible enzymes, nitric oxide synthase (iNOS) and cyclo-oxygenase (COX-2) (Fushia *et al.*, 2000; Takashi *et al.*, 1993). Cyclo-oxygenase (COX-1) is expressed in many tissues, such as the gastric mucosa and kidney. Hence, inhibition of COX-1 reduces the basal production of cyclo-protective PGE1 and PGE2 in the stomach, which can cause the formation of gastric ulcers. It is an interesting observation that of 500 plants extracts tested for COX-2 inhibition; only about 10% have been reported to be active. Compounds that selectively inhibit COX-2 are reported to have fewer side effects. Cyclo-oxygenases catalyse the conversion of arachidonic acid and prostaglandins in a two-step process, i.e. COX-1 and COX-2, have very similar active sites. A single amino acid difference between two enzymes is generally critical for the selectivity of many COX inhibitory drugs (Taylor and Vanstaden, 2001; Robak and Gryglewski, 1996; McLeod, 2001; Ringborn *et al.*, 2001). A similar patent claiming COX-2 inhibition is the triterpenoid, glycyrrhetinic acid (Takashi *et al.*, 1993).

A US patent comprising mixtures of 12 plants from families such as Menispermaceae, Gramineae, Rosaceae, Rutaceae, Leguminosae, Araliaceae, Stemonaceae, Celastraceae, Oleaceae and Asteraceae, are used in a combination for treating osteoarthritis and rheumatoid arthritis (Hou, 1999). In another combination of at least three plants from a group of seven herbs, the preferred composition contains *Tanacetum parthenium*, *Curcuma longa*, and *Zingiber officinale* and inhibits both arthritis and gout (Moore, 1998). Another US patent on *Zanthoxylum simulans*, claims the isolation of fat-soluble alkaloids, chelerythrine, dihydrochelerythrine, oxochelerythirine, *N*-acetylanonanine, skimmiarine and fagarine from the roots, berries and stem bark on extraction with menthol. A menthol ointment prepared with other plant products has been claimed to be effective in rheumatism (Rudolf and Gyorgy, 1988). The patent claim is useful in anaemia due to viral and bacterial infection with rheumatoid arthritis and in combination with *ibuprufen* in the treatment of joint inflammation (Theodore, 1988). It is reported that the mechanism associated in this type of anaemia is believed to be due to an increase in red cell destruction while the synthesis was comparable to normal. It is generally accepted that in such cases activated macrophages T-lymphocytes play an important role in inflammatory processes (Banerjee, 2001).

A Japanese patent on *Eucalyptus* oil, yielding physiologically active compounds namely, EK and EA from the buds, exhibits antiinflammatory activity (Takeda, 1981) and a patent on the alkaloid, berberine from *Berberis vulgaris* (Terukai *et al.*, 1978), also falls under this category. Also, a protopine alkaloid has an analgesic and curare like activity and morphine like action, claims a Polish patent secured on plant *Cheldonium majus* (Leon *et al.*, 1987). A patent claim from the Netherlands on an herbal drug, containing a unique combination of five plants *Humulus lupus*, *Passiflora incarnata*, *Mentha piperita*, *Melissa officinalis* and *Galium*

varum, is effective in conditions such as arthritis and rheumatism. Also, claims the patent, the addition of diazepam for synergistic action of various medicinal plants (Johannes and Marie, 1984). The hydrolysis product of saponins obtained from soyabeans or *Stachybotrys* cultures is useful for controlling autoimmune and rheumatic diseases claims a German patent (Masanao *et al.*, 1979). Another German patent claim on *Rosmarinus* essential oil in combination with *Capsicum* and camphor resulted in the antiinflammatory as well as musculo- skeletal traumas medicament (Hans, 1980; Meinhard *et al.*, 1981). Rosemary essential oil exhibits strong antiinflammatory activity in the rat paw oedema. In the case of a US patent the addition of essential oil enhanced the antiinflammatory activity and showed a 28.6% enhancement of inhibition of carrageenan-induced inflammation. A combination of *Curcuma* compounds was itself shown to exhibit biological activity (Liang, 1991; Oci, 1992). A French patent on *Eucalyptus globules* claims that the oil may be more effective in inflammations caused by infections and is used in a dermatological composition (William, 1980). Catechin, a phenolic compound from the leaves of *Uncaria gambir*, is claimed in a Belgian patent to be antiinflammatory (Georges *et al.*, 1988) and a fraction of it inhibited leucocyte and neutrophil migration induced by carrageenan-induced inflammation (Mackay, 2001). It may also inhibit the release of TNF-alpha, interleukin and other secondary response inflammations (Viana *et al.*, 1997).

Skin inflammations under the eyes and puffiness ascribed to it are treated with emulsified compositions of *Euphrasia* plant extracts admixed with extracts of plants such as butcher-broom, horse chestnut, calendula, hamamelis, horse tail, peach, lady's mantle, ivy, chamomilla and comfrey (Mausner, 1993). A Romanian patent on *Hamamelis virginiana* in combination with horse chestnut, the active constituent of which is the triterpenic saponin, aescin, claims a venotropic ointment active against varicose veins (Emanoil *et al.*, 1978). In such cases, the effect of the extracts was possibly due to inhibition of the release of the mediators of inflammation. *Hamamelis virginiana* has been reported to exhibit an antiphlogistic effect in the croton oil ear oedema test. It is likely due to the presence of proanthocyanidins (Mackay, 2001).

Some patented products contain plants in various combinations, for example, a South African patent claim on an Ayurvedic drug describes the preparation of 'Arenil' (3–15 g/kg) for the treatment of rheumatoid arthritis by admixing the leaves of *Withania somnifera*, *Curcuma longa*, *Inula racemosa*, *Paedaeria foetida* and *Boswellia serrata* with zinc, bala (*Sida acuta*), garlic and Himalayan wild cherry (*Prunus cerasoides*) (Joshi, 1995). A US patent claim describes a similar method for treating musculo-skeletal disease such as rheumatoid arthritis and osteoarthritis in animals (Patwardhan, 1996), wherein a combination of compounds isolated from *Curcuma* spp. alone has been claimed as an antiinflammatory (Liang, 1991; Oci, 1992). A Hungarian patent claims to have formulated an ointment, containing menthol, thymol, plantain and peppermint extracts, thyme flower extracts and camphor. The formula in the form of a suspension has been found to be useful in the treatment of rheumatism (Rudolf and Gyorgy, 1988). A Chinese patent claim contains different plant extracts (from root, bark, bulb and peels) mixed with a gel prepared from chitosamine and pulverized pigskin, along with tortoise plastron, borneol and potassium aluminium sulphate. The product is claimed to be useful as an antiinflammatory substance and artificial skin and to promote skin healing (Baocheng *et al.*, 1989).

A Japanese firm (Sunstar Corporation) has secured a patent on an extract of *Luffa cylindrica*, along with glycyrrhetinic acid and its salt plus glycyrrhizinic acid, allantoin and salicylic acid, formulated in an ointment having a lasting antiinflammatory effect. It has also been shown to be useful for sunburn treatments (Mitsuaki *et al.*, 1992). The roots of *Glycyrrhiza glabra* yield glycyrrhetin in urea solution or in sodium benzoate solution in which the solubility of the compound increases. Minophages Pharmaceutical Company has a claimed patent on the antiinflammatory activity of the compound in urea solution (Moore, 1998). Mitusi Toatsu Chemicals Incorporation has secured a patent on the root of *Glycyrrhiza* infected with *Agrobacterium*, for which the seeds of *Glycyrrhiza uralensis* are cultivated in an *Agrobacterium rhizogens* ATCC 15834 and propagated as a calform free medium. These produce hairy roots containing 1.18–2.98% glycyrrhizin (Ushio, 1990). A separate patent for the isolation of pure glycyrrhizin from licorice is available (Maruzen Chemical, 1981). Also, patents are secured on compounds isolated from licorice as antitussives, analgesics and antipyretics (Muneaki and Kenzo, 1977; Mahato *et al.*, 1992). A Russian patent claim on solutions of licorice obtained after separation of glycyrrhizic acid yields glycyrrham as a triammonium salt (Manyak and Muravev, 1984). A Japanese patent claims to have isolated a forskholin derivative from *Coleus forskholi*, which exhibited skin ulcer inhibitory properties (Makoto *et al.*, 1991). An active compound from neem (*Azadirachta indica*) extract showing antiulcer activity against gastroduodenal ulcer *in vivo* and *in vitro* in experimental models was isolated and obtained a US patent (Bandyopadyay, 1998).

Non-steroidal antiinflammatory drugs (NSAIDS) act by inhibition of the synthesis and actions on prostaglandins. As alternatives to NSAIDS, plant chemicals are available for arthritis, muscle-sprain and other inflammatory processes. They are used in complementary and alternative medicines. Under this category a number of patents have been claimed that yield pain relieving chemicals from plants such as grape seed (Rudolf and Gyorgy, 1988), feverfew (Tomer, 2001), bromelain (Massimiliano, 1983), boswellia (Joshi, 1995), turmeric (Liang, 1991) and Devil's claw (Elie, 1988). Some essential oils such as eucalyptus oil (William, 1980), rosemary oil (Hans, 1980; Meinhard *et al.*, 1981) lavender and millefolia oil (Sorin *et al.*, 1979), pine (Genchiro *et al.*, 1992), clove (Junyi *et al.*, 1989) and myrrh (Baocheng *et al.*, 1989) etc. are used as mixed formulations.

Duality in patent claims on plants showing antiinflammatory activity has been noticed in many European patents emanating from France, Germany, Romania, Poland and the Netherlands. A French patent claim on *Tabernae montana* spp., describes the isolation of alkaloid constituents that are useful as antivirals, and also, admixed in medicaments for nervous disorders, respiratory depression and polio virus (type IV) diseases (Louisette and Odile, 1969), similarly, other plant

patents of French origin, namely *Alkanna tinctorius* has been shown to be antibacterial (Phillippe and Rene, 1981). Bromelains from Bromeliaceae such as pineapple have been described as an antiinfectious, analgesic and homeostatic agents (Antoinette and Jean, 1968). In the case of *Hamamaelis viriginiana*, along with *Aesculus hippocastanum*, constituents show activity against varicose veins and haemorrhoids (Emanoil *et al.*, 1978). A French patent on *Hedra helix* constituents, concerns antitussive and spasmolytic activities (Pierre, 1968). In the case of a US patent claim on *Chrysanthemum americanum*, a flavonoid compound and a saponin derivative of echinocystic acid have shown to be antiinflammatory, analgesic and capillary protective. Compounds are reported to inhibit arachidonic acid metabolism and prostaglandin synthetase.

Harpagophytum procumbens is recommended for arthritis treatment, in the form of tablets prepared by admixing with *Berberis*, *Bryonia* and *Rhus toxicodendron* (Rex, 1983). *Harpagophytum* extracts containing harpagoside; admixed with zinc and selenium has been described as analgesic, antirheumatic and antiinflammatory (Elie, 1988). There is a curare like activity claim on *Chrysantellum indicum*, yielding a triterpene possessing analgesic and capillary protecting activity (Henri *et al.*, 1978). Soya saponins exhibit properties useful for the treatment of nephritis. An analgesic activity has been attributed to the Polish patent secured on celandine root, *Cheldonium majus* (Leon *et al.*, 1987). A Romanian patent on *Plantago lanceolata* and *Berberis vulgaris* claims them to be analgesic and antiulcer, respectively, as well as being antiinflammatory (Terukai *et al.*, 1978).

Japan appears to be following the trends of European nations in the patenting of antiinflammatory plants. *Glycyrrhiza glabra* has been patented for analgesic, antitussive and antipyretic activities (Muneaki and Kenzo, 1977). Similarly, *Prunus persica* and *Aconitum chinense* yield analgesic and antiinflammatory compounds (Taiho Pharmaceuticals, 1983). Composite mixtures of berberine and glycyrrhizinate are claimed as antiulcer and antiinflammatory medicaments (Terukai *et al.*, 1978; Jeanne, 1985). *Rabdosia rubescens* and *Luffa cylindrica* are claimed separately for antitumour (Taiho Pharmaceuticals, 1982) and sunburn treatments (Mitsuaki *et al.*, 1992), respectively. Iodinated peppermint oil, claim a Japanese patent, is useful for wounds and haemorrhoids (Ryoichi, 1979). A Canadian patent on artemisinin, dihydroartemisinin and its derivatives has been patented for haemorrhoid treatment (Carl, 1991). A US patent claims that *Ceanothus thyrisiflorus* leaves and buds are reported to be active against poison oak irritation and inflammation (Frederick, 1985).

The use of herbal medicines is becoming the subject of scrutiny and strict controls in Europe, mainly because the evidence for traditional use is not always reliable (Kingston, 2001). However, the international community has realized that global genetic resources and the indigenous knowledge associated with their use are of importance (Baker *et al.*, 1995). European countries are filing patents claiming one or more biological activities. In the USA, stringent requirements for safety and effectiveness data have discouraged research on these generally unpatentable botanicals; yet, it has spent nearly 50 million dollars to stress the importance of clinical trials in alternative medicine (Tyler, 1997; Embler, 1998). *Panax ginseng*, *Withania somnifera*, *Eucalyptus*, rosemary, devils claw and turmeric, are patented for anticancer/antitumour activity (Darshan and Doreswamy, 1998) by different countries, and have also had patents secured as antiinflammatory agents. The association between chronic inflammation and further development into cancer is known, and it is probably at the time of cell proliferation, where the manifestation of tumour growth by inflammation is likely to be triggered by tissue injury. A decline in glucocorticosteroids levels is in inverse relationship to the increase in incidence of cancer and other degenerative diseases. Licorice reduces the breakdown of cortisol and its diterpenoid fraction glycyrrzin has been shown to increase the antiinflammatory action of steroids (McLeod, 2001). In India, preliminary investigations into the scientific mode of action of a few herbs known as 'Rasayanas' were established for haemorrhoids and fistulas (Dahanukar *et al.*, 2000).

CONCLUSION

Our analysis of 50 antiinflammatory patents reveals that all the claims have recognized the existence of effective traditional remedies for inflammatory disorders from Ayurveda, Siddha in Southern Asia and Unani tibb in Arab regions together with folklore medicines in Asian, African and Latin American countries. The dual nature of the plant patent claims by different countries is somewhat puzzling, because, patent claims on a single plant for two or more physiologically active constituents possessing curative properties may not reflect the same activity/activities in traditional knowledge, and may create confusion in IPR related disputes.

The WIPO accords recognition to traditional knowledge system and informal innovations. Our observations reveal that research and development efforts using medicinal plants are narrowing the knowledge gap between traditional and scientific use of plants in various antiinflammatory diseases. Despite reports that more than 685 plant species are available for treatment of various inflammatory diseases only 5%–6% of plants have been patented to validate the use of plant materials as a commercial source for drug development. As more and more multinational companies are vying with one another to achieve break through in the area of drug development, they have been targeted for claims of biopiracy. With the advent of combinatorial chemistry, many research and development organizations buy synthetic chemicals for their screening programmes at low cost rather than obtaining them from natural sources, which provides a shorter lead time (Wood and Scoot, 2001). However, what is needed are rapid screening techniques, structure based design, and combinatorial chemistry for drug development under new innovations which will share the profit of products derived from indigenous plants, where traditional knowledge forms the base.

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