An overview on anti-inflammatory properties and chemo-profiles of plants used in traditional medicine

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Plant drugs have been the major source for treatment of diseases for a long time. They have been used in traditional medicine on the basis of experiences and practice. With the advent of modern systems of medicine need has been felt to investigate the active constituents present in these plants. Various molecules have been isolated, characterized and tested for their related pharmacological activities. The active molecules have provided significant leads in the development of more effective synthetic molecules. Inflammation is the major condition associated with various diseases. Rheumatoid arthritis is one of the challenging disorders associated with inflammatory conditions. Various molecules have been isolated from plant drugs which have been proven very effective in such conditions. For example: a potent anti-inflammatory analgesic molecule Aspirin was developed from Salicin, a compound isolated from bark of *Salix alba* Linn. This paper provides an overview on the recent findings on some plants having anti-inflammatory activity and chemical constituents isolated from them.

Introduction

Inflammation is a natural response of the mammalian body to a variety of hostile agents including parasites, pathogenic microorganism, toxic chemical substances and physical damage to tissue. The process associated with the inflammatory response are complex but important aspects which have been exploited for screening of anti-inflammatory compound are the various functions of neutrophils, the metabolic products of arachidonic acid and the role played by reactive oxygen species (ROS)[1]. Rheumatoid arthritis (RA) is a common chronic and systemic autoimmune disorder characterized by inflammation of the synovial joints and concomitant destruction of cartilage and bone[2].

Discovery of potent non-steroidal anti-inflammatory drugs (NSAIDs) with very low or no gastrointestinal (GI) side effects is area of prime interest. The use of most commonly prescribed drug from analgesics such as aspirin now a days have been limited due to their potential side effects like severe gastric disorders. With introduction of cyclooxygenase-2 (COX-2) inhibitors problem of GI side effects is overcome up to certain level[3-5].

As a result of the inherent problems associated with the current non-steroidal as well as steroidal anti-inflammatory agents, there is continuous search especially from natural sources for alternative agents. Several herbal medicines constitute a potentially important avenue leading to novel therapeutic agents for inflammation and RA that may not only prevent structural damage of arthritic joints caused by tissue and bone breakdown, but also be safe, relatively inexpensive, highly tolerated and convenient for many patients[6,7].

Herbal remedies for inflammatory disorders

All modern medicines are derived originally from traditional herbal sources. These have evolved to produce the conventional medicine, which uses both synthetic drugs and isolated natural compounds. Herbal medicines are popular among the public and improvements in their formulation have resulted in a new generation of phytomedicines that are more potent than before. Since time immemorial, various herbs and their derived compounds have been used in

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the treatment of inflammation and related disorders like rheumatism. This paper highlights on the chemo-profiles of some herbal medicines used for treating inflammatory disorders and recent developments in various herbal species (Plate 1) having potent anti-inflammatory activity. The chemical structures of major phytoconstituents responsible for the anti-inflammatory potential are enlisted in figure 1 (1-85). Table 1 gives a comprehensive overview of the phytoconstituents of medicinal plants with anti-inflammatory potential.

The plant species studied for their anti-inflammatory activity along with their chemical constituents are described below:

1. *Achillea millefolium Linn. (Asteraceae)*

Aqueous and alcoholic extracts of Yarrow i.e. *A. millefolium* are used in traditional medicine internally in the treatment of gastro-intestinal and hepato-biliary disorders and as an antiphlogistic drug. It is used externally in case of skin inflammations and for wound healing. While a topical anti-inflammatory activity of the sesquiterpenes has already shown being caused by inhibition of the arachidonic acid metabolism, other mechanisms of action might also contribute to the antiphlogistic activity of the drug. The three main flavonoids present in the crude extract and enriched in the flavonoid fraction are rutin (Fig.1.1), apigenin-7-*O*-glucoside (Fig. 1.2) and luteolin-7-*O*-glucoside (Fig. 1.3). The crude plant extract, and two fractions enriched in the dicaffeoylquinic acids (Fig. 1.4, 5, 6) and the flavonoids inhibit human neutrophil elastase (HNE) as well as the matrix metalloproteinases (MMP-2 and -9), which are associated with anti-inflammatory

process *in vitro* studies[8] and gives further insights into the pharmacological activity of *Achillea* and confirm the traditional application as antiphlogistic drug. The *in vitro* antiphlogistic activity of *Achillea* is at least partly mediated by inhibition of HNE and MMP-2 and-9[8].

2. *Alchornea cordifolia* (Schum. & Thonn.) Muell.-Arg. (Euphorbiaceae)

A. cordifolia has been widely used throughout Africa to treat diseases such as dermatitis, asthma, hepatitis, splenomegaly, vaginitis, metritis and colitis. The ethanol fraction from hexane extract of leaves exhibits potent anti-inflammatory activity. The two alkaloids, diisopentenyl guanidine (Fig. 1.7) and triisopentenyl guanidine (Fig. 1.8) exhibit a higher anti-inflammatory activity. Also, some phytoconstituents like β-sitosterol (Fig. 1.9), daucosterol (Fig. 1.10), di (2-ethylhexyl) phthalate (Fig. 1.11) have been reported in the leaves of the herb and their topical anti-inflammatory activity. From the root bark extract, β-sitosterol, daucosterol, acetyl aleuritolic acid (Fig. 1.12), and two above mentioned guanidine alkaloids were isolated. All these compounds could not totally account for the topical anti-inflammatory activity of the herb so the possibility of synergistic action could not be ruled out[9].

3. *Aspilia africana* (Pers.) C.D. Adams (Asteraceae)

It is commonly referred to as Hemorrhage plant due to its ability to stop blood flow from fresh wounds. The plant is also used for traditional treatment of malaria symptoms in East and Central Africa. Germacrene D (Fig. 1.13), α-pinene and
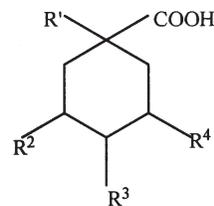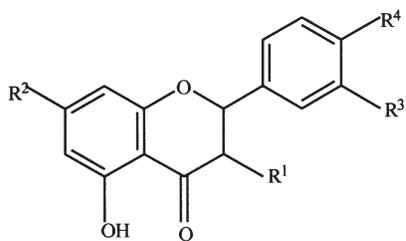

Bacopa monnieri   *Gardenia jasminoides*   *Geranium pratense*
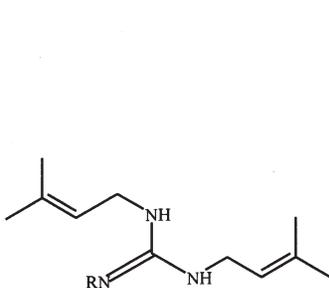
Plate 1—Some of the medicinal plants having anti-inflammatory activity

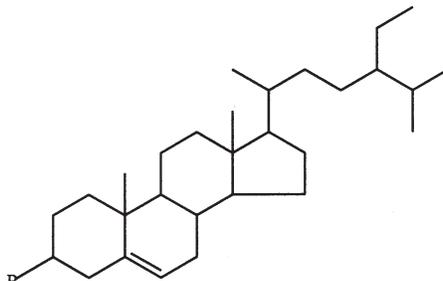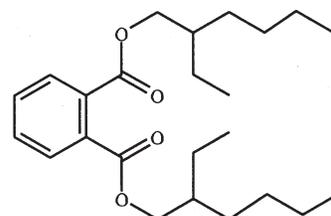**Dicaffeoylquinic acid (DCQA)**

	R¹	R²	R³	R⁴
(1) Rutin	-O-rutinose	OH	OH	OH
(2) Apigenin-7 O-glucoside	-O-glucose	H	OH	H
(3) Luteolin-7-O-glucoside	-O-glucose	OH	OH	H

	R¹	R²	R³	R⁴
(4) 3,4-DCQA	OH	caffeoyl	caffeoyl	OH
(5) 3,5-DCQA	OH	caffeoyl	OH	caffeoyl
(6) 4,5-DCQA	OH	OH	caffeoyl	caffeoyl

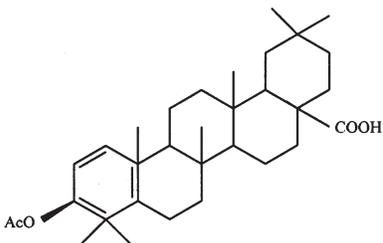**(7)** R=H **di-isopentenyl guanidine**

(9) R = H **β – sitosterol**
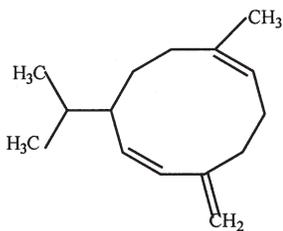**(10)** R = Glucose **Daucosterol**

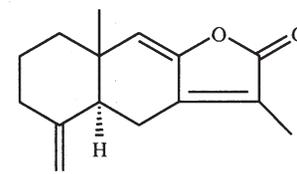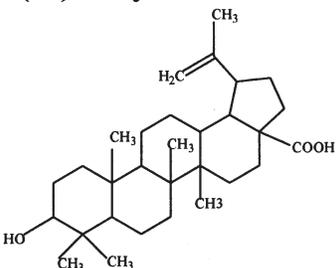**(11) di(2-ethylhexyl)phthalate**

(8) R= **triisopentenyl guanidine**

(12) Acetylaleuritolic acid

(13) Germacrene D

(14) Atractylenolide I

(15) Betulinic acid
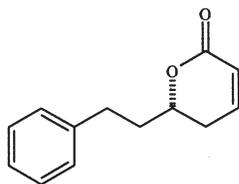
(16) Goniothalamin
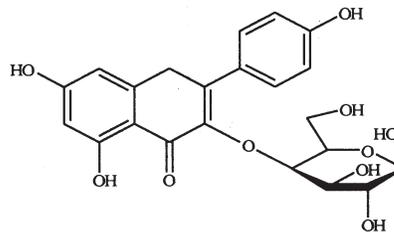
(17) Kaempferol-3-O-α-d-galactoside
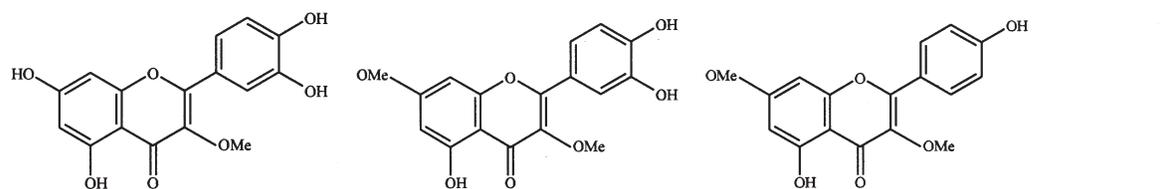
(18) 3-*O*methylquercetin **(19) 3, 7-*O*-dimethylquercetin** **(20) 3, 7-*O*-dimethylkaempferol**
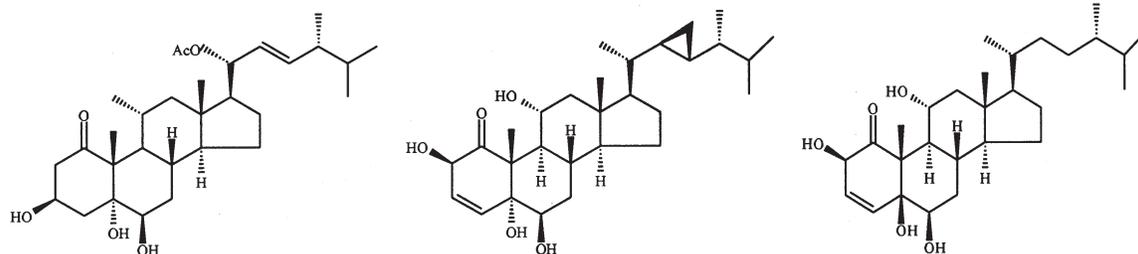
(21) Stoloniferones R **(22) Stoloniferones S** **(23) Stoloniferones T**
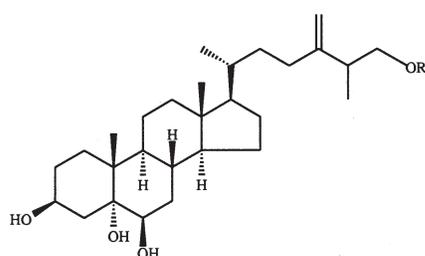
(24) (25*S*)-24-methylenecholestane-3 β, 5 α, 6 β -triol-26-acetate
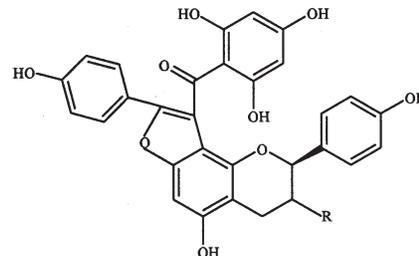
(25) R= H Daphnodorin A
(26) R= OH Daphnodorin B
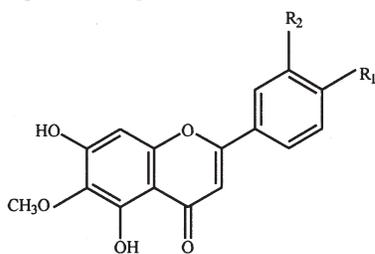
	R_1	R_2
(27) Nepectin	OH	OH
(28) Jaceosidin	OH	OCH$_3$
(29) Hispidulin	OH	H
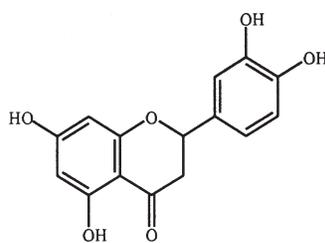
(30) Eriodictyol
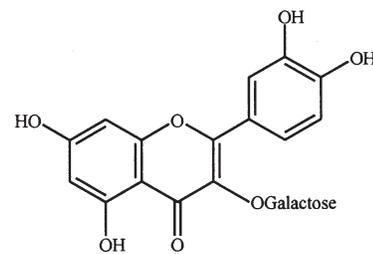
(31) Hyperoside
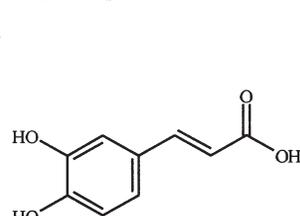
(32) Caffieic acid
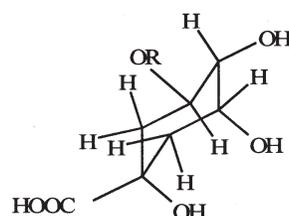
(33) R=caffeoyl
Chlorogenic acid
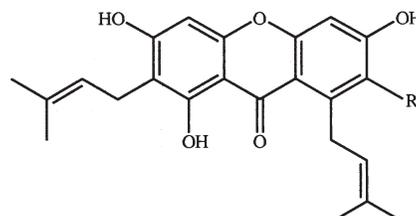
(34) R=OCH$_3$ α-mangostin
(35) R=OH   γ-mangostin
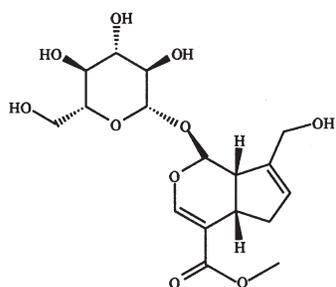
(36) Geniposide
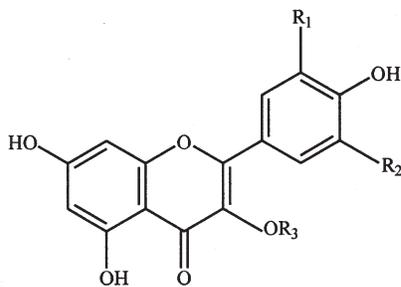
(37 – 44)

	R_1	R_2	R_3
(37)	H	H	β-galactopyranose
(38)	H	H	β-galactopyranose
(39)	OH	H	β-glucopyranose
(40)	OH	H	β-galactopyranose
(41)	H	H	β-glucopyranose
(42)	OH	H	(2''-O-galloyl)- β-glucopyranose
(43)	OH	H	(2''-O-galloyl)-β-galactopyranose
(44)	OH	OH	(2''-O-galloyl)- β-glucopyranose
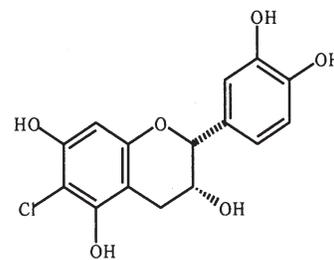
(45) 4(-)-6-chloro-epicatechin
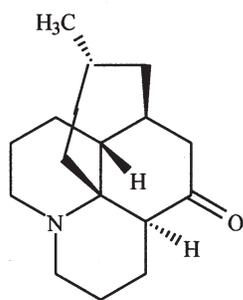
(46) Lycopodine
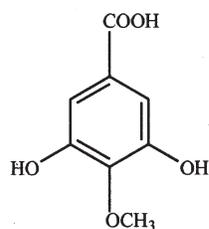
(47) 4-*O*-methylgallic acid
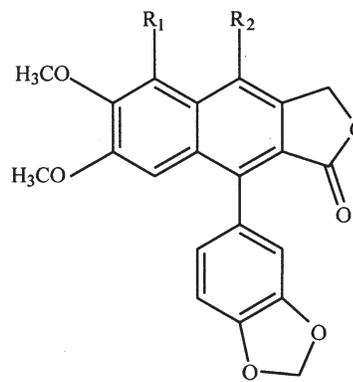
	R_1	R_2
(48) Phyllamyricine	OCH₃	H
(49) Justicidin B	H	H
(50) Diphyllin	H	OH

(51) Piperovatine

(52) Piperlonguminine

	R_1	R_2	R_3	R_4
(53)	OH	CH_2OH	CH_3	Glc⁻Rha-Xyl
(54)	OH	COOH	CH_3	Glc⁻Rha-Xyl
				Api
(55)	=O	COOH	CH_3	Glc⁻Rha-Xyl
				Api
(56)	OH	CH_2OH	CH_3	Glc⁻Rha-Xyl
				Api
(57)	OH	CH_2OH	CH_3	H
(58)	OH	COOH	CH_2OH	H

(59) R = $_3$HCO **21α-Methylmelianodiol**

(60) R = $_3$HCO **21β- Methylmelianodiol**

(61) Cacalol   **(62) Cacalone**   **(63) Cynaropicrin**   **(64) Saussureamine A**
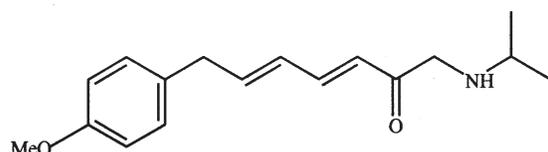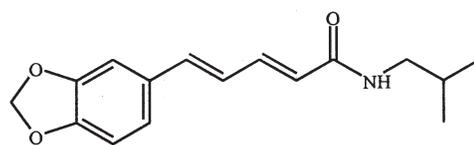
(65) Saussureamine B   **(66)Costrunolide**   **(67) Dehydrocostrus lactone**   **(68) Sedumosine**
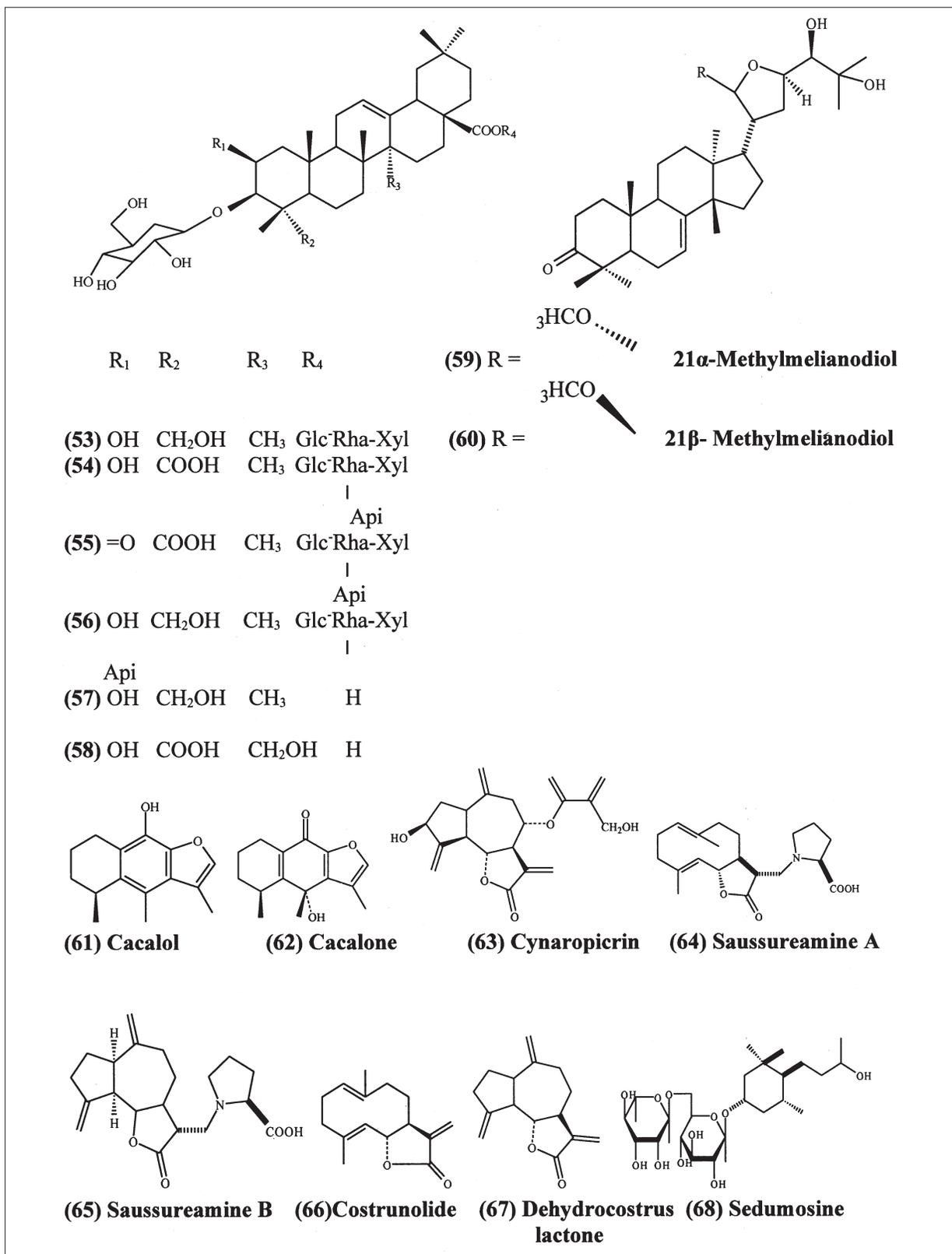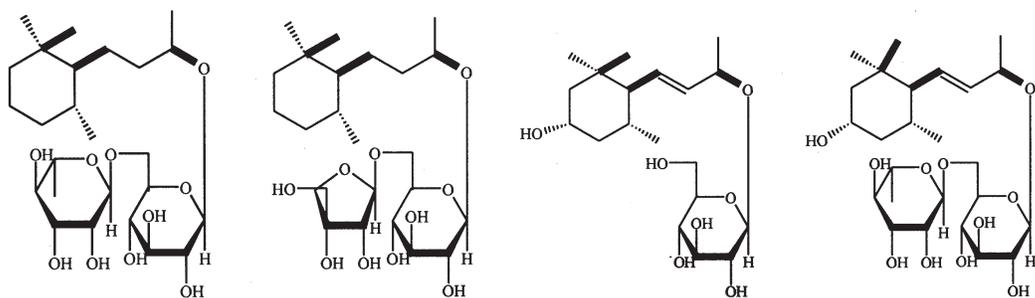
(69) Sedumosine E2   **(70) Sedumosine E3**   **(71) Sedumosine F1**   **(72) Sedumosine F2**
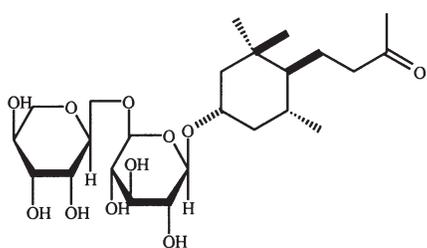
(73) Sedumosine G
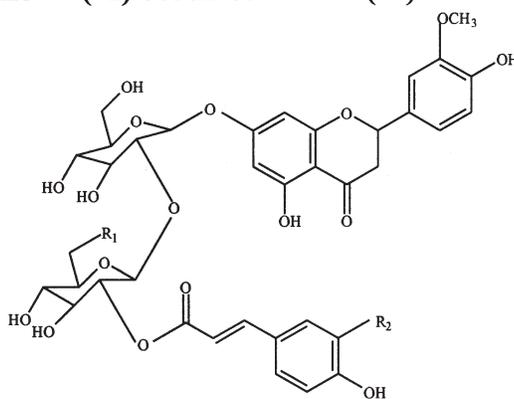
(74) R$_1$: OAc R$_2$: OH **Ozturkosides A**
(75) R$_1$: OH   R$_2$: OH **Ozturkosides B**
(76) R$_1$: OAc R$_2$: H **Ozturkosides C**
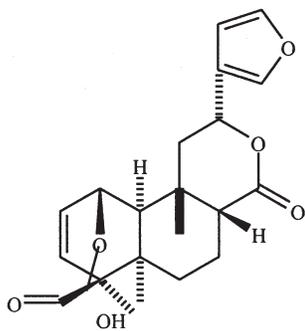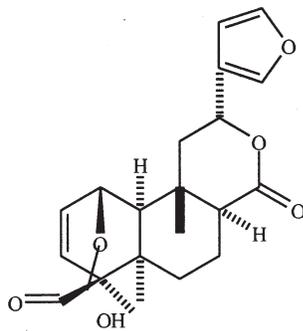
(77) Columbin   **(78) Isocolumbin**   **(79) Febleucin**
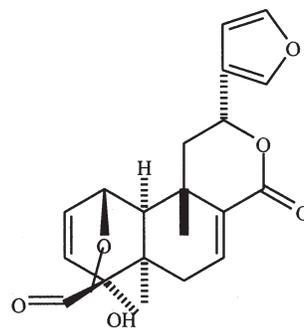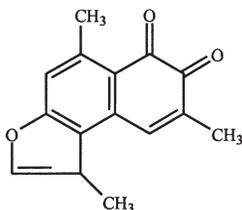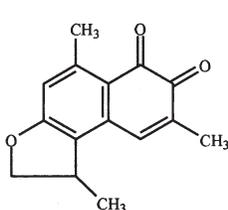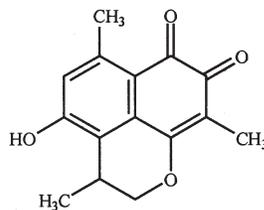
(80) Thespone   **(81) Mansonone – D**   **(82) Mansonone – H**   **(83) Thespesone**
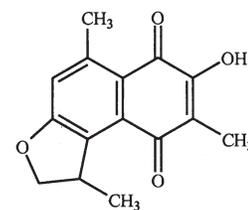
(84) Monocrotaline   (85) Supinine
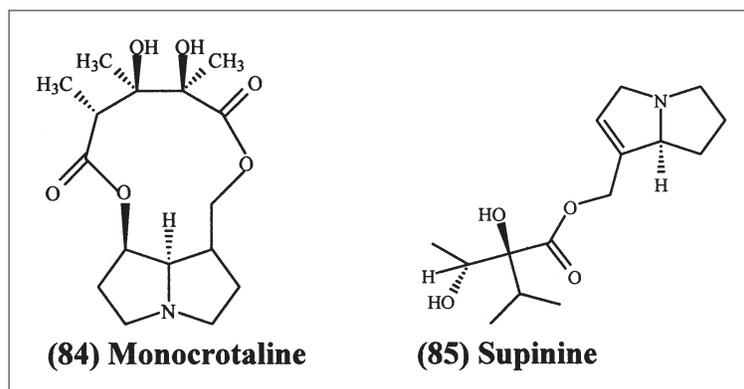
Fig. 1 (1-85)—Chemical structures of some phytoconstituents responsible for anti-inflammatory activity

Table 1—Chemo-profiles of selected anti-inflammatory medicinal herbs

S. No.	Name of herb	Family	Part used	Phytoconstituents isolated	Reference
1	*Achillea millefolium* Linn.	Asteraceae	Whole plant	Essential oil, sesquiterpenes, phenolic compounds such as flavonoids and phenolcarbonic acids, Rutin (Fig.1.1), apigenin-7-*O*-glucoside (Fig.1.2) and luteolin-7-*O*-glucoside (Fig.1.3), dicaffeoylquinic acid (Fig.1.4, 5, 6)	8
2	*Alchornea cordifolia* (Schum. & Thonn.) Muell.- Arg.	Euphorbiaceae	Leaves	Two alkaloids viz. diisopentenyl guanidine (Fig.1.7) and triisopentenyl guanidine (Fig.1.8), also β-sitosterol (Fig.1.9), daucosterol (Fig.1.10), and di (2-ethylhexyl) phthalate (Fig.1.11)	9
			Root bark	β-sitosterol, daucosterol, acetyl aleuritolic acid (Fig.1.12), diisopentenyl guanidine and triisopentenyl guanidine	
3	*Aspilia africana* C.D. Adams	Asteraceae	Leaves	Terpenoids, Germacrene D (Fig.1.13), α-pinene and limonene have been isolated from the essential oil of the leaves. Also β-sitosterol (Fig.1.9)	10
4	*Atractylodes macrocephala* Koidz.	Asteraceae	Rhizomes	Sesquiterpenes and acetylenic compounds, Atractylenolide I (Fig.1.14)	11
5	*Bacopa monnieri* (Linn.) Penn.	Scrophulariaceae	Whole plant	Triterpene, betulinic acid (Fig.1.15)	12
6	*Bryonopsis laciniosa* (Linn.) Naud. syn. *Bryonia laciniosa* Linn.	Cucurbitaceae	Whole plant	Goniothalamin (Fig.1.16), punicic acid and lipids	13
7	*Calluna vulgaris* Linn.	Ericaceae	Whole plant	3, 5, 7, 8, 4′-pentahydroxyflavone-4′-*O*- β -$_D$ glucoside, callunin, quercetin-3-*O*- β - $_D$ - galactoside, isorhamnetin-3-*O*- β - $_D$ -galactoside, and chlorogenic acid, kaempferol-3-*O*- β - $_D$- galactoside (Fig.1.17)	14
8	*Cistus laurifolius* Linn.	Cistaceae	Leaves	3-*O*-methylquercetin (Fig.1.18), 3, 7′-*O*-dimethylquercetin (Fig.1.19), 3, 7′-*O*-dimethylkempferol (Fig.1.20), quercetin-3-*O*-α-rhamnoside,1-(4-hydroxy-3-methoxy phenyl)-2-[4-(3-α-L rhamno-pyranoxypropyl)-2 methoxy phenoxy]-1,3-propanediol	15
9	*Clavularia viridis* Quoy & Gaim.	Clavularidae	Soft coral	Stoloniferones R, S and T (Fig.1.21, 22, 23) and (25*S*)- 24-methylenecholestane-3β,5α,6β-triol-26-acetate (Fig.1.24)	16

Contd.

Table 1—Chemo-profiles of selected anti-inflammatory medicinal herbs--*Contd*

S. No.	Name of herb	Family	Part used	Phytoconstituents isolated	Reference
10	*Daphne pontica* Linn.	Thymelaeaceae	Aerial parts, roots	Daphnodorins (Fig.1.25, 26)	17
11	*Eupatorium arnottianum* Griseb.	Asteraceae	Whole plant	Cadinene derivatives, a *p*-coumaroyl acid esters several 6,7-dimethoxyflavones and 2-hydroxy-4-(2_-hydroxypropoxy)-acetophenone Nepetin (Fig.1.27), jaceosidin (Fig.1.28) and hispidulin (Fig.1.29)	18
			Ethanolic extract	Eriodyctiol (Fig.1.30), hyperoside (Fig.1.31), rutin, nepetin, caffeic (Fig.1.32) and chlorogenic (Fig.1.33) acids	
12	*Garcinia mangostana* Linn.	Guttiferae; Clusiaceae	Rind of fruit	a- and c-mangostins (Fig.1.34, 35)	19
13	*Gardenia jasminoides* Ellis	Rubiaceae	Fruit	Geniposide (Fig.1.36)	20
14	*Geranium pratense* Linn. subsp. *finitimum* (Woronow) Knuth	Geraniaceae	Whole plant	Quercetin 3-*O*-α- arabinopyranoside (Fig.1.37), kaempferol 3-*O*-*β*-galactopyranoside (Fig.1.38), quercetin 3-*O*-*β*-glucopyranoside (Fig.1.39), quercetin 3-*O*-*β*-galactopyranoside (Fig.1.40), kaempferol 3-*O*-*β*- glucopyranoside (Fig.1.41), quercetin 3-*O*-(2″-*O*-galloyl)-*β*-glucopyranoside (Fig.1.42), quercetin 3 -*O* -(2″-*O*-galloyl) –*β* - galactopyranoside (Fig.1.43), myricetin 3- *O*-(2″-*O*-galloyl)-*β* glucopyranoside (Fig.1.44) and (−)-6-chloroepicatechin (Fig.1.45)	21
15	*Lycopodium clavatum* Linn.	Lycopodiaceae	Aerial parts	Lycopodine (Fig.1.46)	22
16	*Phyllanthus polyphyllus* Linn.	Euphorbiaceae	Whole plant	4-O-methylgallic acid (Fig.1.47), 2-(hydroxymethyl)-6, 7, 8-trimethoxy-4-(3, 4-methylenedioxy-phenyl)-3-naphthoic acid-γ-lactone (phyllamyricin C) (Fig.1.48), 2-(hydroxymethyl)-6, 7-dimethoxy-4-(3, 4-methylenedioxy-phenyl)-3-naphthoic acid γ-lactone (Justicidin B) (Fig.1.49), 1-hydroxy-2-(hydroxymethyl)-6,7-dimethoxy-4-(3,4-methylenedioxy-phenyl)-3-naphthoic acid- γ-lactone (diphyllin) (Fig.1.50)	23
17	*Piper ovatum* Vahl	Piperaceae	Whole plant	Piperovatine (Fig.1.51) and piperlonguminine (Fig.1.52)	24
18	*Polygala japonica* Houtt	Polygalaceae	Whole plant	Saponins (Fig.1.53-58)	25
19	*Poncirus trifoliata* Rafin.	Rutaceae	Fruit	21α-methylmelianodiol (21α-MMD) (Fig.1.59) and 21β-methylmelianodiol (21β-MMD) (Fig.1.60)	26
20	*Psacalium decompositum* (Gray) Rob. et Brett.	Asteraceae	Roots and rhizomes	Sesquiterpenic compounds (furanoeremoplilanes), such as cacalol (Fig.1.61), cacalone (Fig.1.62), maturin, maturinone and maturone, etc.	27
21	*Saussurea costus* (Falc.) Lipschitz	Asteraceae	Whole plant	Cynaropicrin (Fig.1.63), Saussureamines A and B (Fig.1.64, 65), costunolide (Fig.1.66) and dehydrocostus lactone (Fig.1.67)	28
22	*Sedum sarmentosum* Bunge	Crassulaceae	Whole plant	Sedumosides E1 (Fig.1.68), E2 (Fig.1.69), E3 (Fig.1.70), F1 (Fig.1.71), F2 (Fig.1.72) and G (Fig.1.73)	29
23	*Sideritis ozturkii* Aytac & Aksoy	Lamiaceae	Aerial parts	Ozturkosides A, B and C (Fig.1.74, 75, 76), Campesterol, stigmasterol and β-sitosterol hypolaetin- 8-glucoside and 5-*O*-demethylnobiletin	30

Contd—

Table 1—Chemo-profiles of selected anti-inflammatory medicinal herbs--*Contd*

S. No.	Name of herb	Family	Part used	Phytoconstituents isolated	Reference
24	*Sphenocentrum jollyanum* Pierre	Menispermaceae	Root hair	Furanoditerpenes- Columbin (Fig.1.77) (major), isocolumbin (Fig.1.78) and fibleucin (Fig.1.79) (both minor)	31
25	*Thespesia populnea* Soland ex Correa	Malvaceae	Leaves and bark	Thespone (Fig.1.80), mansonone-D (Fig.1.81), mansonone-H (Fig.1.82), thespesone (Fig.1.83)	32
26	*Trichodesma amplexicaule* Roth	Boraginoideae	Roots	Monocrotaline (Fig.1.84), supinine (Fig.1.85) as pyrrolizidine alkaloids, hexacosane, α-amyrin, lupeol	33

limonene have been isolated from the essential oil of the leaves. The crushed leaves of *A. africana* have been used for patients suffering from rheumatic pains in traditional medicines. The hexane extract relieves rheumatism and offer the additional advantage of suppressing inflammatory response initiated by the tissue injury. The extract suppresses both the early and later phases of the acute inflammatory response. The extract inhibited the release or actions of the various chemical mediators such as histamine, 5-HT, kinins and prostanoids known to mediate acute inflammation. Mainly the sterols [β-sitosterol (Fig. 1.9)] and isolated terpenoids are responsible to exhibit anti-inflammatory activity in this herb[10].

4. *Atractylodes macrocephala* **Koidz.** (Asteraceae)

The plant has been used traditionally against the problems like anorexia, edema, etc. The rhizomes of *A. macrocephala* are rich in sesquiterpenes and acetylenic compounds. Atractylenolide I (Fig. 1.14) was found to be an active compound in different anti-inflammatory assays. When atractylenolide I was tested for inhibitory activity against 5-lipoxygenase and cyclooxygenase-1, it showed no remarkable inhibitory effect against either of these enzymes[11].

5. *Bacopa monnieri* **(Linn.)** **Penn.** (Scrophulariaceae)

In Ayurvedic medicine, it is extensively used to treat various inflammatory conditions such as bronchitis, asthma and rheumatism. The anti-inflammatory action of ethanolic extract of *B. monnieri* could be postulated via calcium antagonism. Calcium channel blockers are known to suppress the inflammation, prostaglandin E1, bradykinin and serotonin. The presence of anti-inflammatory activity of this plant may be attributed to the triterpene, betulinic acid (Fig. 1.15) isolated from this plant[12].

6. *Bryonopsis laciniosa* **(Linn.)** **Naud.** (Cucurbitaceae)

The plant *B. laciniosa* syn. *Bryonia laciniosa* Linn. is found wildly in India, Philippines and some parts of Africa. It has been used in the treatment of jaundice, inflammation and fever. Goniothalamin (Fig. 1.16), punicic acid and lipids have been isolated from the whole plant. The chloroform extract of leaves exhibited significant anti-inflammatory activity in acute and chronic inflammatory experimental animal models. The extract exhibits its anti-inflammatory action by means of either inhibiting the synthesis, release or action of inflammatory mediators, viz. histamine, serotonin and prostaglandins in rats. The extract showed significant anti-inflammatory activity in chronic conditions by inhibiting the increase in the number of fibroblasts and synthesis of collagen and mucopolysaccharides during granuloma tissue formation. The extract drastically reduced the migration of neutrophils and leukocytes in mice[13].

7. *Calluna vulgaris* **(Linn.) Hull** (Ericaceae)

Ethnobotanical use of *C. vulgaris* (Heather) has been recorded as antirheumatic as well as for the treatment of gout in European societies. A homoeopathic remedy prepared from the fresh branches is prescribed in the treatment of rheumatism, arthritis and insomnia. Phytochemical studies have shown the presence of phenolic components. The ethyl acetate extract of aerial parts and its main flavonoid glycoside, kaempferol-3-*O*-β-d-galactoside, exerted significant *in vivo* anti-inflammatory and antinociceptive activities, which support the ethnobotanical use of this plant in traditional medicines. It has been stated that kaempferol-3-*O*-β-D-galactoside (Fig. 1.17) possess a remarkable anti-inflammatory activity. Various kaempferol glycosides also show significant inhibitory activities on TNF-α production and nitric oxide (NOS) release. In

particular, this herb has exhibited the most potent cyclooxygenase inhibition. The flowers of this herb exert effect on arachidonic acid metabolism. The acetone extract of flowers inhibits lipoxygenase (LOX) enzyme potently and further it leads to the isolation of ursolic acid as an active anti-lipoxygenase component. Ursolic acid inhibits 5-LOX better than 12- and 15-LOX[14].

8. *Cistus laurifolius* **Linn.** (Cistaceae)

In Turkish folk medicine, the leaves of *C. laurifolius* are used externally as an effective remedy against several inflammatory ailments including rheumatism and renal inflammations. For relieving rheumatic pain a warm decoction of leaves is used as a bath or wilted leaves are externally applied on joints. The leaves showed activity against inflammatory cytokines, interleukin 1-α as well as prostaglandins (PG).

To evaluate folkloric claims, Kupeli and Yesilada[15] studied the effects of the extracts and fractions from the leaves with non-woody branches of *C. laurifolius* using two *in vivo* models of inflammation in mice. Model one was based on observed potent inhibitory activity against carrageenan-induced hind paw oedema and the second model used was acetic acid-induced, increased vascular permeability model. Through bioassay-guided fractionation and isolation procedures three flavonoids; 3-*O*-methylquercetin (1.18), 3,7-*O*-dimethylquercetin (1.19) and 3,7-*O*-dimethylkaempferol (1.20) were isolated as the potent antinociceptive and anti-inflammatory principles from leaves. The potency of these flavonoids was found to be equal to that of Indomethacin, a well-known anti-inflammatory agent, without inducing any apparent acute toxicity or gastric damage. These compounds were also reported to possess potent antihepatotoxic activity against acetaminophen-induced liver damage in mice which is important from the viewpoint of safety evaluation of these compounds[15].

9. *Clavularia viridis* **Quoy & Gaim.** (Clavularidae)

The soft coral *Clavularia* has afforded many types of bioactive prostanoids, terpenoids and steroids. Fractionations of the Formosan soft coral *C. viridis* resulted in the isolation of four new steroids, stoloniferones R,S,T (Fig. 1.21-23) and (25*S*)-24-methylenecholestane-3β,5α,6β-triol-26-acetate (Fig. 1.24). These compounds significantly reduced the levels of the iNOS protein compared to the control. Chin-Hsiang Chang *et al* performed *in vitro* anti-

inflammatory assay on lipopolysacharide (LPS) stimulated Murine RAW 264.7 macrophages to prove the activity. Compounds stoloniferone T and (25*S*)-24-methylenecholestane-3β, 5α, 6β-triol-26-acetate significantly reduced the levels of the COX-2 protein compared with the control cells stimulated with LPS[16].

10. *Daphne pontica* **Linn.** (Thymelaeaceae)

In the historical documents, *Daphne* species were proposed in cancer treatment since the time of Aphrodisias (AD 2nd century). Flavonoid type constituents, daphnodorins (Fig. 1.25, 26), were isolated as one of the antitumour components from the roots. Several *Daphne* species have been used against inflammatory disorders. In Traditional Chinese Medicine, several *Daphne* species have been frequently added in formulations prescribed against inflammatory disorders; i.e., *D. genkwa* Sieb. & Zucc. to dispel edema, *D. acutiloba* Rehder for wounds and bruises, *D. tangutica* Maxim. for treatment of rheumatoid arthritis, seeds and barks, rarely leaves, of *D. mezereum* Linn. in chronic rheumatism, gout and inflammations in the lymph tissue. Traditionally, aerial parts and roots of *D. pontica* have been used for the treatment of rheumatic pain and inflammatory ailments. The extract evidently inhibits the production of PGE_2 and IL-1β. Furthermore, it remarkably reduced the content of NO (nitric oxide) and inactivated the activity of iNOS[17].

11. *Eupatorium arnottianum* **Griseb.** (Asteraceae)

Eupatorium arnottianum Griseb. (*Clavel*, *tuji*) is an herb that grows in the North-East, Centre of Argentina and South of Bolivia. It is used by rural populations of Santa Salta, Argentina for gastric pains and by *Kallawaya* healers from the Bolivian altiplano against asthma, bronchitis, colds, topically in plasters for bone fractures and dislocations. *E. arnottianum* has been widely used in phytotherapy as hepatoprotective, and against fever and rheumatism, different kind of pains and inflammation, headaches. Three anti-inflammatory compounds identified as nepetin (Fig. 1.27), jaceosidin (Fig. 1.28) and hispidulin (Fig. 1.29) have been isolated from the dichloromethane extract of aerial parts of this herb. Among them, nepetin is the most active one. Chemical analysis of the ethanolic extract of this herb revealed the presence of eriodyctiol (Fig. 1.30), hyperoside (Fig. 1.31), rutin, nepetin, caffeic (Fig. 1.32) and chlorogenic acids (Fig. 1.33). Some

6-methoxylated flavones have been found to be active in different experimental models. B-ring substituted flavones of this type are capable of inhibiting cotton-pellet induced granuloma and carrageenan edema in rats. An important inhibitory effect in the NF κB luciferase assay exerted by nepetin and jaceosidin has been reported which explains anti-inflammatory activity of these compounds[18].

12. *Garcinia mangostana* **Linn.** (Guttiferae; Clusiaceae)

The fruit rinds of *G. mangostana* (Mangosteen) L have been used as a traditional medicine for the treatment of trauma and skin infections. The xanthones, α-and γ-mangostins (Fig. 1.34, 35) are major bioactive compounds found in the fruit hulls of the mangosteen. The possibility that xanthones exhibit their biological effects by blocking inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expressions, It is suggested that the two mangostins decrease protagandin (PG)E2 levels through inhibition of COX-2 activity and NO production. It is suggested that α-mangostin shows a more potent inhibition of PGE2 release than either histamine or serotonin. On the other hand, γ-mangostin inhibits edema, which has also been previously reported[19].

13. *Gardenia jasminoides* **Ellis** (Rubiaceae)

The fruit of *G. jasminoides* has been included in traditional medicine formulations for the treatment of inflammation. Geniposide (Fig. 1.36), a major irioid glycoside of the fruit shows inhibition of both 5-lipoxygenase and ovalbumin-induced junction permeability. Genipin, the aglycone of geniposide shows inhibition of apoptosis and potent, topical anti-inflammatory activity. Genipin has a stronger acute anti-inflammatory activity than Geniposide. Genipin effectively inhibits the activation of NF-κB by blocking the degradation of IκB. Since the activation of NF-κB is required for the induction of cyclooxygenase 2 expression, Genipin is believed to inhibit acute inflammation by blocking cyclooxygenase 2 expression. Genipin and Geniposide both markedly decrease the content of nitrite. The inhibitory effect of Genipin on NO production may correlate with its stronger anti-inflammatory activity. A lower activity of Geniposide in the acute anti-inflammatory conditions and a reduction in NO production may be due to its delayed transport of cells, since it contains a single glucose

unit in its chemical structure. Therefore, Genipin would be an ideal starting point, for the development of a new NSAID with fewer side effects[20].

14. *Geranium pratense* subsp. *finitimum* (Woronow) Knuth (Geraniaceae)

G. pratense subsp. *finitimum* has been used to alleviate rheumatism traditionally in China. The aqueous extract of this herb shows presence of flavonoids mainly quercetin 3-*O*-α-arabinopyranoside (Fig. 1.37), kaempferol 3-*O*-β-galactopyranoside (Fig. 1.38), quercetin 3-*O* β-glucopyranoside (Fig. 1.39), quercetin 3-*O*-β-galactopyranoside (Fig. 1.40), kaempferol 3-*O*-β-glucopyranoside (Fig. 1.41), quercetin 3-*O*-(2″-*O*-galloyl)-β-glucopyranoside (Fig. 1.42), quercetin 3-*O*-(2″-*O*-galloyl)-β-galactopyranoside (Fig. 1.43), myricetin 3- *O*-(2″-*O*-galloyl)-β glucopyranoside (Fig. 1.44) and (−)-6-chloroepicatechin (Fig. 1.45). Aqueous extract from the aerial parts and two flavonoid mixtures isolated from it, quercetin-3-*O*-α-arabinopyranoside and kaempferol-3-*O*-β-galacto-pyranoside, and quercetin-3-*O*-β-glucopyranoside and quercetin-3-*O*-β-galactopyranoside significantly inhibited the formation of the edema. Esra K¨upeli and colleagues studied effectiveness of aqueous herbal extract, its fractions and isolated constituents against carrageenan induced inflammation. The results were compared with Indomethacin as a standard drug. The activity has been found in the late phase of the edema, possible activity might be due to the inhibition of prostaglandin release[21].

15. *Lycopodium clavatum* **Linn.** (Lycopodiaceae)

L. clavatum commonly known as Club moss has been reported to be used for wound healing effect. According to ethno-botanical survey, the leaf decoction of this plant has been used against muscle pain and rheumatism in Malaysia. According to the study carried out by Orhan *et al*, four extracts prepared with petroleum ether, chloroform, ethyl acetate and methanol as well as the alkaloid fraction from the aerial parts of *L. clavatum* using acetic acid-induced increase in capillary permeability assessment in mice revealed that only the chloroform extract and the alkaloid fraction displayed marked anti-inflammatory effect as compared to Indomethacin. Bioassay-guided fractionation of the alkaloid fraction revealed that the alkaloidal-type of compounds might possibly be responsible for the anti-inflammatory activity of the extract, which supports the folk

medicinal utilization of the plant. Alkaloidal fraction of aerial parts mainly Lycopodine (Fig. 1.46) has shown remarkable anti-inflammatory activity[22].

16. *Phyllanthus polyphyllus* **Linn.** (Euphorbiaceae)

It is a small shrub used as an anti-inflammatory folk medicine in tropical and subtropical regions in India and Sri Lanka. Four compounds, one benzenoid [4-*O*-methylgallic acid (Fig. 1.47)] and three arylnaphthalide lignans [phyllamyricin C (Fig. 1.48), justicidin B (Fig. 1.49) and diphyllin (Fig. 1.50)] isolated from whole plant showed growth inhibitory effect on production of NO and cytokines (TNF-α and IL-12). Since TNF-α and IL-12 were known as the main pro-inflammatory cytokines secreted during the early phase of acute and chronic inflammatory diseases, such as asthma, rheumatoid arthritis, septic shock, the use of *P. polyphyllus* as anti-inflammatory remedy in traditional medicine may be attributed by these compounds[23].

17. *Piper ovatum* **Vahl** (Piperaceae)

Leaves of *P. ovatum* are used in traditional Brazilian medicine for the treatment of inflammation and as an analgesic. *P. ovatum* possesses inhibitory properties that are specific to cyclooxygenase-1, which in turn are important mediators of the development of inflammatory diseases. The lack of an inhibitory effect of the hydroalcoholic extract of leaves on pleurisy, in contrast to the inhibitory effect on ear edema, may be attributable to several factors, including the action of the extract on the different inflammatory mediators involved. The amide fractions of extract piperovatine and piperlonguminine showed the greatest inhibition of topical inflammation induced by croton oil and might be useful as powerful topical anti-inflammatory agents[24].

18. *Polygala japonica* **Houtt** (Polygalaceae)

P. japonica has long been used traditionally for the treatment of various inflammatory diseases, such as acute tonsillitis, nephritis, etc. in China. The chemical studies have reported triterpenoid saponins and flavones from this herb. Saponins (Fig. 1.53, 56 and Fig. 1.57) inhibited both phases of the edema. Saponin (Fig. 1.53) is the most potent compound, with inhibitory activity even better than the reference compound. However, saponin (Fig. 1.58) showed less potent activity and reached its maximal anti-inflammatory effects later as compared to saponins

(Fig. 1.53 & 1.57). It has been shown that the mechanism of saponins in anti-inflammatory activity may be mediated by inhibiting the activation of nuclear factor-kB, thus resulting in decreased expression of NF-kB-regulated proteins such as inducible nitric oxide synthase (iNOS)[25].

19. *Poncirus trifoliata* **Rafin.** (Rutaceae)

The hot-water extract of *P. trifoliata* fruits has been used in traditional medical practice for a long time, such as in the treatment of stomach disorders. Additionally, the anti-inflammatory and anti-allergy actions of the fruits of *P. trifoliata* have also been reported. Two isomers of 21-methylmelianodiol [21α-MMD (Fig. 1.59) and 21β-MMD (Fig. 1.60)] isolated from the fruits of this herb have potential as treatments for inflammatory diseases and have been found to inhibit NO production. Both compounds attenuate lipopolysaccharide (LPS)-induced protein and mRNA expressions of iNOS and COX-2. Therefore, the inhibition of NF-κB transcriptional activity can contribute to the inhibitory effect of 21α-MMD and 21β-MMD on iNOS, COX-2, TNF-α and IL-1β genes expression. 21α-MMD shows a significant inhibitory effect on the production of NO, and attenuates the synthesis of proteins of iNOS and COX-2 as well as the mRNA levels of iNOS, COX-2 and IL-1β. Therefore, it is suggested that the inhibitory effect of 21α-MMD might, at least in part, be due to its inhibition of iNOS, COX-2 and IL-1β mRNA expressions, and consequently of NO, PGE2 and IL-1β synthesis/release[26].

20. *Psacalium decompositum* **(Gray) Rob. et Brett.** (Asteraceae)

Both roots and rhizomes of *P. decompositum* (syn. *Cacalia decomposita* A. Gray) have been utilized by the Mexican population against pain and rheumatism. Phytochemical studies revealed that the herb contains various sesquiterpenic compounds (furanoeremoplilanes), such as cacalol, cacalone, maturin, maturinone and maturone, etc. Cacalol (9-hydroxy-3,4,5-trimethyl-5,6,7,8-tetrahydronaphto(2,3-b)furan) and cacalone are the most abundant constituents of the herb. Cacalol (Fig. 1.61) and cacalone (Fig. 1.62) present in hexane extract of the herb shows distinct anti-inflammatory activity. Cacalol only reduces the inflammation at first hour after its administration, showing some connection with histamine function in the inflammatory process. On the contrary cacalone showed the highest anti-

inflammatory activity at the end of the test (about 5 hours), indicating some association with PG inflammatory function. The effect produced by cacalone probably involves other inflammatory mediators besides COX, such as histamine, 5-hydroxytryptamine, bradykinine or nitric oxide, all of which have been reported in Carrageenan-induced edema. Thus, the beneficial effects attributed to *P. decompositum* in traditional medicine can be related with the anti-inflammatory activity of cacalol and cacalone[27].

21. *Saussurea costus* **(Falc.) Lipschitz** (Asteraceae)

It is frequently used in Korean traditional prescriptions for inflammatory diseases. The methanol extract of *S. costus* exhibited more than 50% of inhibition of the cytokine induced neutrophil chemotactic factor (CINC) induction. A sesquiterpene lactone isolated from the methanolic extract of the herb exhibits dose dependent inhibition on the lipopolysaccharide (LPS)-stimulated NRK-S2-E cells of rat kidney. Dehydrocostus lactone isolated from the herb inhibited the production of nitric oxide by suppressing inducible nitric oxide synthase enzyme expression. The total ethanol extract exhibited more than 50% of inhibition on tumor necrosis factor (TNF)-alpha production. The principal inhibitory component of the herb is cynaropicrin and its inhibitory effect is mediated through conjugation with SH-groups of target proteins. It also potently attenuates the accumulation of NO released from lipopolysaccharide and interferon-gamma. Cynaropicrin (Fig. 1.63) may participate in the inflammatory response by inhibiting the production of inflammatory mediators and the proliferation of lymphocytes and its inhibitory effect is mediated through conjugation with sulfydryl groups of target protein(s). Saussureamines A and B (Fig. 1.64, 65) in addition to costunolide (Fig. 1.66) and dehydrocostus lactone (Fig. 1.67) do not inhibit inducible NO synthase (iNOS) enzyme activity, but they inhibited both induction of iNOS and activation of NF-kappa B [(Ref.28)].

22. *Sedum sarmentosum* **Bunge** (Crassulaceae)

It is a perennial herb widely distributed on the mountain slopes in Oriental countries, has been traditionally used for the treatment of certain inflammatory diseases. It has been frequently used for the treatment of chronic inflammatory diseases. Recently, six new megastimane glycoside,

sedumosides E1, E2, E3, F1, F2 and G (Fig. 1.68-73), were purified from the whole plant. Activity of *S. sarmentosum* partly arises from its prevention from the release of inflammatory mediators at the first stage. Suppressive effect of this herb on the production of NO has been confirmed. With the assumption that the suppression of NO production by herb is being caused by a diminishment in the iNOS level, the herb concentration-dependently suppressed iNOS induction without changes in the levels of β-actin, an internal control, indicating the specific inhibition of iNOS expression. However, at the concentrations capable of reducing the NO production in the activated macrophages has been unable to modulate expression of COX-2. This fact suggests that the herb might exhibit its anti-inflammatory activity independent of COX-2 [(Ref.29)].

23. *Sideritis ozturkii* **Aytac. & Aksoy** (Lamiaceae)

It is a traditionally used Spanish folk medicine for its anti-inflammatory and gastroprotective properties to treat certain disorders that are accompanied by inflammation. Several anti-inflammatory compounds have been obtained from *S. ozturkii*, mainly flavonoids and terpenoids. Apart from the flavonoid and diterpen derivatives, sterol fractions have also shown to possess anti-inflammatory activity. Lipid fraction and a sterol fraction composed of campesterol, stigmasterol and β-sitosterol have also been reported as active components. Acetone extract from the aerial parts the herb and the major constituents, ozturkosides A, B and C (Fig. 1.74, 75, 76), isolated from the active acetone extract, possess antinociceptive and anti-inflammatory activity. Ozturkoside C showed notable antinociceptive and anti-inflammatory activities without inducing any apparent acute toxicity or gastric damage. Although the activity of ozturkosides A and B were found insignificant in statistical analysis, some inhibitory effect was observed. Accordingly, it is suggested that these components in phenolic fraction might possibly share the antinociceptive and anti-inflammatory activities together. In spite of a high number of studies reporting the anti-inflammatory and antinociceptive activities of several *Sideritis* species only two flavonoids have been isolated and defined as the active constituents; hypolaetin-8-glucoside and 5-*O*-demethylnobiletin. Hypolaetin-8-glucoside shows very close chemical structure to ozturkoside C both having luteoline type flavone glycoside structure[30].

24. *Sphenocentrum jollyanum* Pierre (Menispermaceae)

The root hair of *S. jollyanum* has been used traditionally in south western Nigeria to treat rheumatism, fever and body pain. During a study by Moody *et al*[31] it was observed that methanolic extract was having remarkable anti-inflammatory activity. Three furanoditerpenes, columbin, isocolumbin and fibleucin (Fig.1.77, 78, 79) isolated from the extract showed significant sustained and dose dependant anti-inflammatory activity. The pattern of anti-inflammatory activity exhibited by this herb tends to suggest that the plant's activity may wholly or in part be mediated by cyclooxygenase enzymes I and II inhibition[31].

25. *Thespesia populnea* Soland ex Correa (Malvaceae)

In southern India and Sri Lanka, the leaves and bark of *T. populnea* are used to produce oil for the treatment of fracture wounds and as an anti-inflammatory poultice applied to ulcers and boils, as a folk medicine. Ethanolic extract of the herb shows anti-inflammatory activity in both acute and chronic models. The phytochemical studies indicated that the ethanolic extract of bark contains alkaloids, carbohydrates, protein, tannins, phenols, flavonoids, gums and mucilage, saponins and terpenes. Four naturally occurring quinines, viz. thespone (Fig. 1.80), mansonone-D (Fig. 1.81), mansonone-H (Fig. 1.82) and thespesone (Fig. 1.83) have been extracted from heart-wood of the herb[32].

26. *Trichodesma amplexicaule* Roth (Boraginaceae)

Traditionally *T. amplexicaule* is used as an emollient and poultice. The roots are pounded into paste used to reduce swelling of joints and leaves are used for rheumatism and arthritis. The main chemical constituents are monocrotaline (Fig. 1.84), supine (Fig. 1.85) as pyrrolizidine alkaloids, hexacosane, α-amyrin, lupeol, non-steroidal and fatty constituents. Terpenoids from the aerial parts of the herb gave reproducible activity against edema and chronic arthritis[33].

Discussion and Conclusion

Plants have played a remarkable role in health care since the ancient times. Traditional plant based medicines still exert a great deal of importance to people living in developing countries and also lead to discovery of new drug candidates[22].

Majority of human population worldwide is getting affected by the inflammation related disorders. It is believed that current analgesia inducing drugs such as opiates and NSAIDs are not useful in all cases, because of their side effects like gastrointestinal irritation, liver dysfunction and many others[4,32]. A number of immuno-suppressing agents and pain relieving agents have been developed based on their inhibition of cyclooxygenase-1 (COX-1), but they cause detrimental side effects on long term administration. Accordingly, selective inhibitors of cyclooxygenase-2 (COX-2) were developed to avoid side effects of COX-1 inhibitors. However, one of these inhibitors has been reported to increase the risk of myocardial infarction and atherothrombotic events. Thus, it is likely that COX-2 inhibitors will not be suitable for the treatment of chronic inflammatory diseases, such as, rheumatoid arthritis[5].

Drug therapy for Rheumatoid Arthritis is based on two principal approaches: symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs). However, most of the currently available drugs are primarily directed towards the control of pain and/or the inflammation associated with joint synovitis, but do little to interfere with the underlying immuno-inflammatory events, and consequently also do little to block the disease progression and reduce cartilage and bone destruction of joints[6].

Accordingly, therapeutic agents suitable for the treatment of chronic inflammatory diseases are highly desirable, which has resulted in an increased interest in complementary and alternative medicines.

Large number of herbal species has been used traditionally or as folk medicines against inflammatory ailments. Many of them have been studied scientifically and proved to be beneficial anti-inflammatory agents. The success has been attained to isolate various single chemical entities responsible for anti-inflammatory activity.

Despite the divergent bioactivities of plant medicines against various diseases, active components of the most plant extracts have not been elucidated thoroughly, due to their complex mixtures containing up to hundreds of ingredients. However the core chemical classes of anti-inflammatory agents from natural sources have been usually reported to engage a vast range of compounds such as polyphenols, flavonoids, terpenoids, alkaloids, anthraquinones, lignans, polysaccharides, saponins and peptides[34,35].

From the exhaustive study done so far, some striking findings come in to light. It has been elucidated that flavonoids are the major anti-inflammatory agents. Some of them act as phospholipase inhibitors and some have been demonstrated as TNF-α inhibitors in different inflammatory conditions. Biochemical investigations have also shown that flavonoids can inhibit both cyclooxygenase and lipooxygenase pathways of the arachidonic metabolism depending upon their chemical structures[36,37].

Quercetin is a bioflavonoid compound that blocks the release of histamine and other anti-inflammatory enzymes. Although human studies with arthritic patients are lacking at this time, anecdotal evidence is strong for this application, as is experimental research investigation. There are no well-known side effects or drug-nutrient interactions for quercetin[38-41].

Alkaloids in asserted skeletal type based on pyridine ring system have been presented with striking anti-inflammatory activity, e.g. Berberine from *Berberis* is a traditional remedy against rheumatism[42].

Curcumin, the principal curcuminoid is the active anti-inflammatory agent found in the spice turmeric. It has been shown to inhibit the activity of the 5-lipoxygenase and cyclooxygenase enzymes, blocking the synthesis of pro-inflammatory eicosanoids (PG-2, LTB-4). It has also been shown to be effective in the treatment of postsurgical inflammation. Curcumin can lower histamine levels and is a potent antioxidant. These factors may also contribute to its anti-inflammatory capabilities. Side effects are rare, but primarily include heartburn and esophageal reflux. As curcumin inhibits the cyclooxygenase enzyme system, it may reduce platelet aggregation and thus may potentiate the effects of anti-coagulant drugs. To date, no bleeding disorders have been reported with curcumin supplementation, but its concurrent use with warfarin or coumadin should be considered a contraindication[38,43-47].

Terpenoids significantly inhibit the development of chronic joint swelling. In Western medicine, the treatment often involves topical application of corticosteroids which are symptomatically effective but have inherent disadvantages. Terpenoids may affect different mechanism relevant to inflammations arising in response to varied etiological factors[16].

White Willow bark extract provides anti-inflammatory phenolic glycosides, such as salicin, which have been shown to be effective in the treatment of arthritis, back pain and other joint inflammatory conditions. These phenolic glycosides are known to inhibit cyclooxygenase, blocking the production of PG-2, and exert a mild analgesic effect. Unlike acetyl salicylic acid (ASA), naturally occurring salicin (salicylic acid) does not irreversibly inhibit platelet aggregation, reducing the potential for a bleeding disorder. White willow bark extract has been shown to be slower acting than ASA, but of longer duration in effectiveness. It is important to realize that besides salicin, white willow bark extract contains other phenolic glycosides, which are also known to possess anti-inflammatory properties[44,48-50].

However, still many herbal folk medicines for inflammation and rheumatism have not undergone through scientific investigations and careful assessment of their toxic effects. Hence, it is a need of time to consider all such folk use based herbal medicines for determining their pharmacological activities, isolating the single drug entity responsible for anti-inflammatory effect and developing suitable formulation, beneficial against inflammatory disorders.

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