The Journal of Phytopharmacology 2014; 3(4): 275-285
Online at: www.phytopharmajournal.com

Review Article

ISSN 2230-480X
JPHYTO 2014; 3(4): 275-285
July- August

Secondary metabolites as anti-inflammatory agents

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Abstract

Inflammation is a complex pathophysiological process mediated by a variety of signaling molecules and can be classified as either acute or chronic. Anti inflammatory drugs are broadly classified into two categories: Steroidal and Non steroidal anti-inflammatory agents (NSAIDs) some of them are no longer used due to their severe adverse effects. Traditionally, people have been using powerful anti-inflammatory plants for thousands of years as part of their diet and pharmaceutical arsenal, and secondary compounds derived from these plants may offer important sources of anti-inflammatory agents.

Keywords: Secondary metabolites, Anti-inflammatory agents.

Introduction

Inflammation is a complex pathophysiological process mediated by a variety of signaling molecules produced by leukocytes, macrophages and mast cells as well as by the activation of complement factors, which bring about edema formation as a result of extravasation of fluid and proteins and accumulation of leukocytes at the inflammatory site.[1] The inflammatory response is, in general, protective and ultimately rids tissues of both the cause and consequences of tissue injury that can accompany host defense.[2] Inflammation as a fundamental response to injury has been recognized for many thousands of years. The Egyptians described abscesses and ulcers, and the Code of Hammurabi (2000 BC) detailed instructions on how to treat abscesses of the eye. The Greek physician, Hippocrates may have been the first to regard inflammation as the beginning of a healing process, introducing words such as edema and erysipelas to describe its symptoms. The first comprehensive description of inflammatory symptoms can be found in De Medicina, written by Aulus Celsus (~25 BC–AD 38) who described the four symptoms of inflammation as rubor, tumor, color, and dolor (redness, swelling, heat, and pain. The fifth sign of inflammation, functiolaesa (impaired function) was added by Galen of Pergamon some 100 years later. [3] Anti inflammatory drugs are broadly classified into two categories: Steroidal and Non steroidal anti-inflammatory agents (NSAIDs). Steroidal Drugs act on the inflammatory cells and the inflammatory mediators. Non Steroidal anti-inflammatory drugs act by inhibiting Cyclooxygenases 1 and 2 (COX- 1 and COX-2).[4] PlantS secondary metabolites have provided an important source of drugs since ancient times and now around half of the practical drugs used are derived from natural sources.[5] and Many of this herbal constituents are being prescribed widely for the treatment of inflammatory conditions.[6]

Secondary metabolites used as anti-inflammatory agents

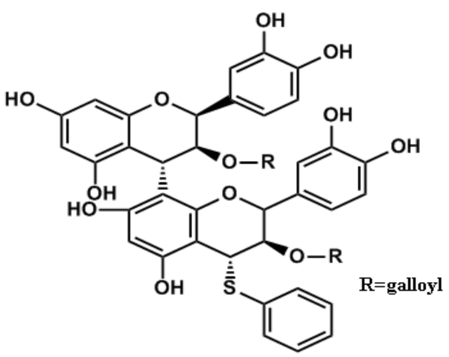
Phenolic compounds

Phenolic compounds are of important pharmacological value, some having anti-inflammatory properties. Different types of phenolic compounds such as flavonoids, condensed tannins, and gallotannins are known to inhibit some molecular targets of pro-inflammatory mediators in inflammatory responses.[7]

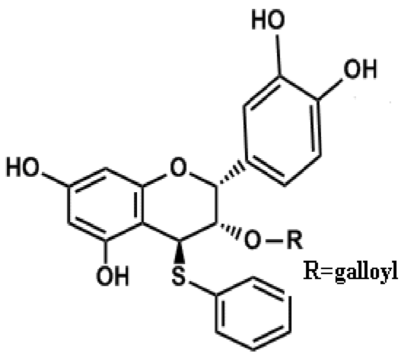
Condensed tannins

Condensed tannins (proanthocyanidins) are essentially derived from (+) gallocatechin, (−) epicatechin, (+) catechin and epigallocatechin, and their derivatives via carbon to carbon (C–C) links.[7] Proanthocyanidins are naturally-occurring plant metabolites, widely available in fruits, vegetables, nuts, seeds, flowers and bark. Proanthocyanidins play important roles at the nutritional and physiological level and in pharmacology for their antioxidant properties. Proanthocyanidins are also associated with a number of biological activities, such as anti-inflammatory, anti-asthmatic, anticancer, antimicrobial, anti-allergy, antihypertensive and cardioprotective. The beneficial effects of proanthocyanidins on human health have been attributed mainly to their strong free radical-scavenging and antioxidant activities.[8] These compounds are antagonists of particular hormone receptors or inhibitors of particular enzymes such as COX enzymes.[7]

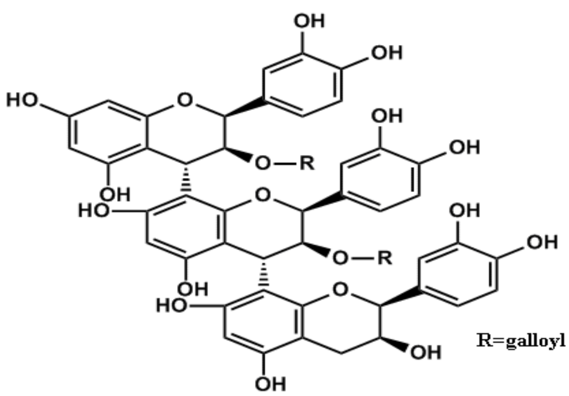
e.g. Proanthocyanidins from grape seeds[9], leucoanthocyanidins from the hot water bark extract of the black spruce, Picea *mariana*[8], and proanthocyanidin with (+) -epicatechin units of ethanol-water extract of *Pyrsonima crassifolia* bark showed a strong anti-inflammatory activity. [10]



3-*O*-galloyl-(+)-epicatechin-[4α→8]-3-*O*-galloyl-



3-*O*-galloyl-(-)-epicatechin-4-benzylthioether



(+) -epicatechin-4α-benzylthioether

Figure-1: proanthocyanidin with (+) -epicatechin units from *Pyrsonima crassifolia*

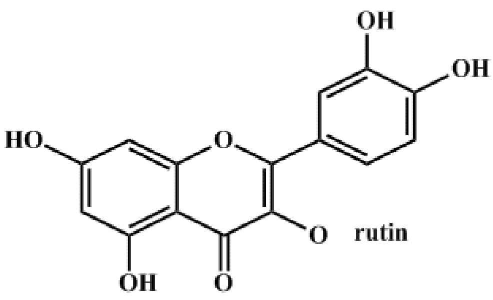
Gallotannins

Gallotannins exert various biological effects ranging from anti-inflammatory to anticancer and antiviral properties. The mechanisms underlying the anti-inflammatory effect of tannins includes the scavenging of radicals and inhibition of the expression of inflammatory mediators, such as some cytokines, inducible nitric-oxide synthase (iNOS), and COX-2. The high amount of the guillotine was detected in *Protea simplex* leaf. [7]

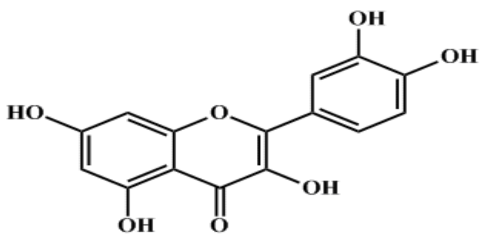
Flavonoids

Flavonoids are polyphenolic compounds that occur ubiquitously in foods of plant origin. Over 4000 different flavonoids have been described, and they are categorized into flavonols, flavones, catechins, flavanones, anthocyanidins and isoflavonoids.

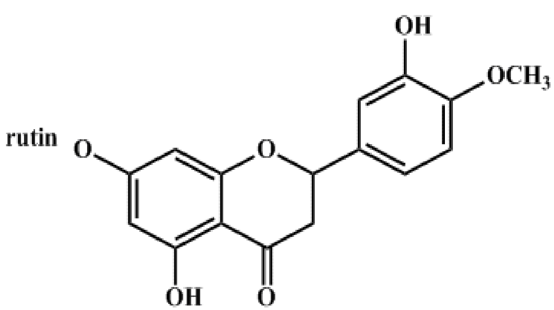
Flavonoids have a variety of biological effects in numerous mammalian cell systems, in vitro as well as in vivo. They have been shown to exert antimicrobial, antiviral, antiulcerogenic, cytotoxic, antineoplastic, mutagenic, anti-inflammatory, antioxidant, antihepatotoxic, antihipertensive, hypolipidemic and antiplatelet activities. [11] Flavonoids are known to act on the inflammatory response via many routes and blockmolecules like COX, ins, cytokines, nuclear factor-κB and matrix metalloproteinases.[7] Flavonoids were investigated in models of inflammation in rats and were found to possess significant activity in both proliferative and exudative phases of inflammation. Flavonoids showed anti-inflammatory activity and inhibited the development of the induced granuloma, mostly when a catechol or guaiacol-like B ring is contained in the compound structure. Some flavonoids, such as quercetin, blocked both the cyclooxygenase and lipooxygenase pathways at relatively high concentrations, while at lower concentrations; the lipooxygenase pathway was the primary target of inhibitory anti-inflammatory activity. A micronized flavonoid complex, consisting of 90% diosmin+ 10% hesperidin (Daflon 500 mg), protected against the formation of perivascular edema and its therapeutic values were determined by its inhibitory activity on the inflammatory process. On the other hand, when administered subcutaneously, hesperidin (hesperetin-7-rutinoside) exhibited significant anti-inflammatory activity on rat paw edema induced by both carrageenan and dextran and on carrageenan pleurisy, without producing the side effects that are caused by other classes of anti-inflammatory drugs. Some authors have reported that flavonoids such as rutin (quercetin-3-rutinoside) and quercetin show antioxidant activity.[11]



Quercetin



Rutin

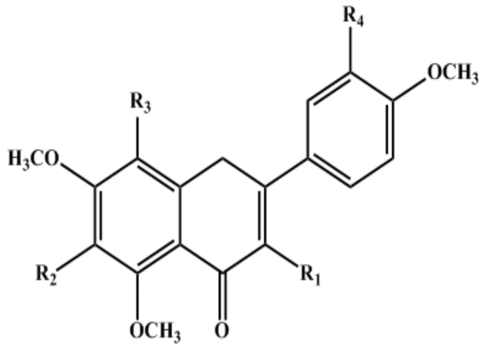


Hesperidin

Figure-2: Some flavonoids with antioxidant activity

Dioclein is a flavonoid (flavanone family) isolated from the roots of *Dioclea grandiflora* Mart. ex Benth. The flavonoid dioclein has significant suppressor activity on the production of the pro-inflammatory mediators (IL-6, TNF-α, CXCL1/ KC, CCL2/JE and NO), by LPS-stimulated macrophages in vitro; has significant reactive oxygen species scavenging activity both in macrophages and cell free systems; and reduction of the concentration of reactive oxygen species in the medium contributes to the inhibitory effects. This combination of inhibitory effects that results in inhibition of inflammation is unique among flavonoids.[12]

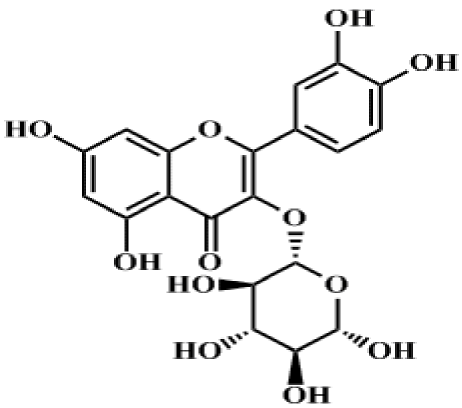
Various flavonoids and polymethoxyflavones from adlay bran (Job's tears, *Coix lachryma-jobi* L. var. ma-yuen Stapf), were reported to have a broad spectrum of biological activity, including cytotoxicity, inducing apoptosis in adipocytes, an anti-inflammatory effect.[13]



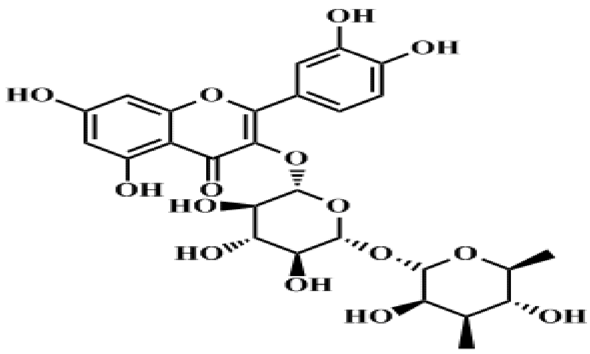
Name	R1	R2	R3	R4
3,4',5,7-tetramethoxyflavone	OCH3	H	H	H
3,3',4',5,7-pentamethoxy-flavone	OCH3	H	H	OCH3
Tangeretin	H	OCH3	OCH3	H
3,5,6,7,8,3',4'-heptamethoxyflavone	OCH3	OCH3	OCH3	OCH3

Figure-3: polymethoxyflavones from adlay bran

Nine flavonoids having better ability for binding to the COX-2 substrates binding site by the scores come from virtural screening. Luteolin, apigenin and scutellarein are flavones, quercetin, myricetin and centaureidin are flavonols, genistein is isofla-vones, isoquercitrin and rutin are flavone glycoside, there are no isoflavones, chalcones and flavanones. Centaureidin and luteolin were found to be the most potential inhibitors of COX-2.[14]



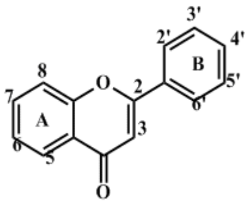
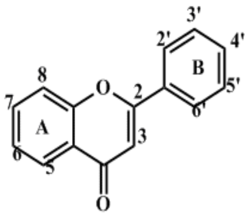
Isoquercitin



Rutin

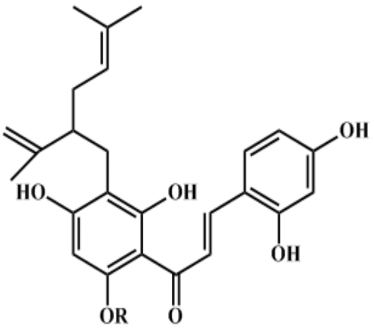
Figure 4: Flavone glycoside

Table 1: Chemical structures of the various flavonoids tested for the inhibitors of COX-2

Chemical formula	Name	Substitution							
		5	6	7	8	2'	3'	4'	5'
Flavone									
	Luteolin	OH	H	OH	H	H	OH	OH	H
	Apigenin	OH	H	OH	H	H	OH	OH	OH
	Scutellarein	OH	OH	OH	H	H	OH	H	H
Flavonol									
	Quercetin	OH	H	OH	H	H	OH	OH	H
	Myricetin	OH	H	OH	H	H	OH	OH	OH
	Genistein	OH	OMe	OH	H	H	OH	OMe	H
	Centaureidin	OH	OME	OH	H	H	OME	OH	H

The antiinflammatory activities of 30 flavonoids isolated from several plants of the Compositae (Asteraceae alt.) family were investigated using carrageenaninduced mouse paw edema and cotton pellet-induced rat granuloma. Flavonoids inhibit the development of the induced granuloma, mostly when a catechol or guaiacol-like B ring is contained in the compound structure, jaceosidin being the most active flavonoid screened.[15]

Among the constituents isolated from the roots of *Sophora flavescens*, the prenylated flavonoids, including sophoraflavanone G, kuraridin and kurarinone were previously found to inhibit eicosanoid producing enzymes such as COX-1, COX-2, 5-lipoxygenase (5-LOX) and 12-LOX. Sophoraflavanone G was also shown to exert in vivo anti-inflammatory activity in several animal models via oral and topical treatment. Additionally, kurarinone was reported to inhibit monocyte chemoattractant protein-1-induced chemotaxis. Taken together, these previous results strongly suggest that the prenylated flavonoid-enriched fraction of this plant material possesses promising anti-inflammatory activity.[16]



Kurarinone R=CH3

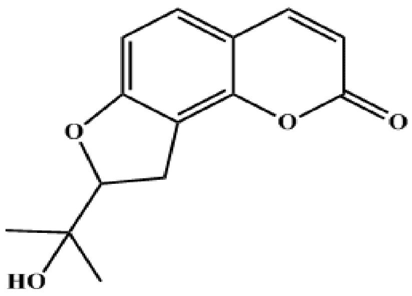
Sophoraflavanone G R=H

Figure 5: prenylated flavonoid from *Sophora flavescens*

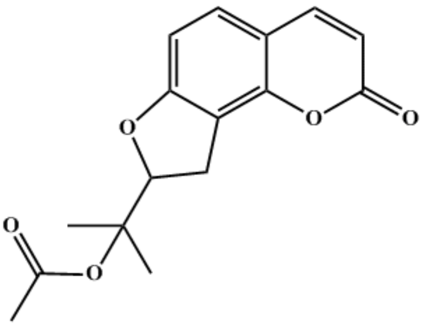
Coumarins

Coumarins represent a vast family of compounds which were naturally found in plants. It has been already reported that several coumarin derivatives have significantly anti-inflammatory and antioxidant activities. Thus, coumarin derivatives could be particularly effective in the treatment of high protein oedemas. It was reported that some coumarins possessed the antioxidant capacity scavenging superoxide anion radicals and some coumarins could inhibit both the lipoxygenase and cyclooxygenase pathways of arachidonic acid metabolism.[17]

Two coumarin derivatives, columbianetin (A) and libanoridin (B) were isolated from *Corydalis* *heterocarpa*[18], and coumarins isolated from *Torresea cearensis, Justicia pectoralis, Eclipta alba, Pterodon polygaliflorus* and *Hybanthus ipecacuanha* showed significant anti-inflammatory activity.[19]



Columbianetin



Libanoridin

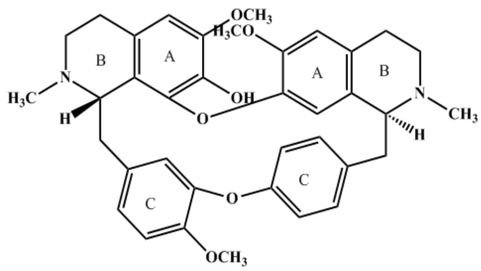
Figure 6: Coumarins isolated from *Corydalis heterocarpa*

Alkaloids

Some alkaloids such as isoquinoline, indole and diterpene are known to have good anti-inflammatory activity.[7]

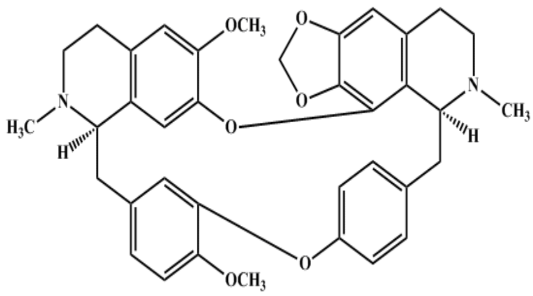
Three types of isoquinoline alkaloids were detected in the roots, barks and branches of Turkish *Berberis* species: protoberberine (berberine, palmatine, jatrorrhizine, columbamine), bisbenzylisoquinoline (berbamine, oxyacanthine, aromoline) and aporphine (magnoflorine) types.[20]

Bisbenzylisoquinoline alkaloids have been used since antiquity in East medicine as major components of some antirheumatic remedies. They also possess antiinflammatory, immunomodulatory and antimalarial activities. Recently, there has been interest in the use of bisbenzylisoquinoline alkaloids as potential antiinflammatory drugs, based on their ability to prevent the synthesis or the action of some proinflammatory cytokines. One of the most investigated bisbenzylisoquinoline alkaloids is tetrandrine and its analogues berbamine and fangchinoline.[21]



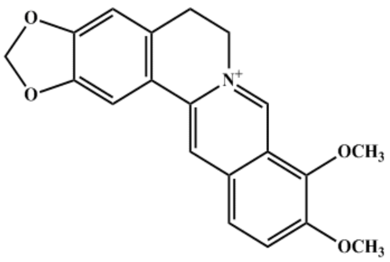
Fangchinoline

Bisbenzylisoquinoline alkaloids Cepharanthine, cycleanine, and isotetrandrine from *Stephania cephararantha* exhibited suppressive effects on in vitro histamine release and nitric oxide production. Cepharanthine was a highly potent inhibitor of HIV-replication in chronically infected monocytic cell line and suppressed the production of inflammatory cytokines and neural cell death. [22]

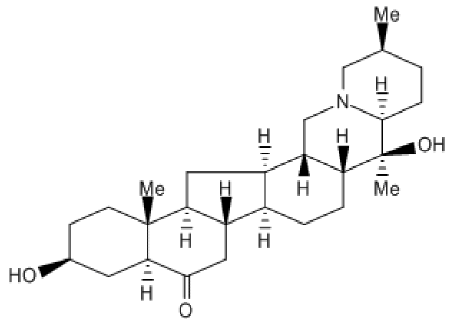


Cepharanthine

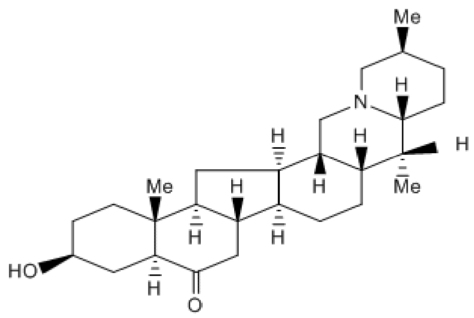
Other alkaloids; Imperialine and chuanbeinone from Bulbus *Fritillariae Cirrhosae* [23] imperialine, imperialine-β-N-oxide, isoverticine, and isoverticine-β-N-oxide from Bulbus of *Fritillaria wabuensis*[24], berberine and 8-hydroxydihydrosanguinarine alkaloids from *Chelidonium majus*[25], were showed significant anti-inflammatory activity.



Berberine



Imperialine



Chuanbeinone

Figure 7: Alkaloids from Bulbus *Fritillariae Cirrhosae*

Saponins

Saponins are steroid or triterpcne glycosides (Some authors distinguish a third group called steroidal amines, which are classified by others as steroidal alkaloids) widely distributed in the plant kingdom that include a large number of biologically active compounds. Saponins isolated from about 50 plants showed anti-inflammatory activity against several experimental models of inflammation in mice and rats. Mechanisms considered included indirect (many saikosaponins) and direct (saikosaponin d and ginsenosides) corticomimetic activity, inhibition of glucocorticoid degradation (glycyrrhizin), inhibition of enzymatic formation and release of inflammation mediators (ginsenosides Rb2, Re, R, saikosaponins a, c, d). Recently, anti-inflammatory activity has been described for two triterpene saponins from *Quercus imbricaria* and a bidesmosidic echinocystic acid glycoside from *Pithecellobium dulce*. A new steroid saponin dracoside was isolated during the search for the anti- rheumatic principle of the roots of *Helleborus purpurascens.* Its antiinflammatory effect could be assigned to a counter-irritation effect.[26]

Three triterpenoid saponins (saponins 1, 4 and 5) with significant anti-inflammatory activity were isolated from *Polygala japonica.*[27] There are a number of reports of saponins with anti-inflammatory properties. Fruticesaponin B, a bidesmosidic saponin with an unbranched saccharide moiety isolated from *Bupleurum fruticescens* L. (Apiaceae), was shown to have the highest anti-inflammatory activity of the all the saponins tested in the mouse oedema assays. In vivo studies on saponins isolated from *Bupleurum rotundifolium* L. (Apiaceae) were reported to have anti-inflammatory activity against both 12-*O*-tetradecanoylphorbol-13-acetate (TPA) induced ear oedema and chronic skin inflammation. Of the seven saponins tested, five were fairly active in reducing the TPA-induced ear oedema. The saponins produced a dose-dependent oedema reduction. Only two saponins were active in reducing the chronic skin inflammation, and also caused a parallel decrease in neutrophile infiltration.

Aescin, a mixture of triterpenoid saponins that forms the major active principle of *Aesculus hippocastanum* L. (Hippocastanaceae), has been shown to have anti-inflammatory, anti-oedematous and venotonic properties.

A novel steroidal saponin isolated from the leaves of *Agave attenuata* Salm-Dyck (Agavaceae) was evaluated for anti-inflammatory activity. The steroidal saponin inhibited the increase in vascular permeability caused by acetic acid, which is a typical model for the first stage inflammatory reaction. However, the activity was not accompanied by an undesirable haemolytic effect and warrants further investigation as an anti-inflammatory drug. The triterpenoid saponin loniceroside C isolated from the aerial parts of *Lonicera japonica* Thunb. (Caprifoliaceae), showed anti-inflammatory activity when tested *in vivo*.

Sterols

Phytosterols and their derivatives are essential components of plant biomembranes and they are biogenetic precursors of numerous metabolites such as plant steroid hormones. Plant sterols have been investigated as an alternative for lowering plasma cholesterol levels, and several studies have shown that they significantly reduce plasma total and LDL cholesterol. Antiatherosclerotic effects of plant sterols are well documented. The anti-atherogenic effects may be due, not only to their cholesterol-lowering activities, but also to other properties, such as effects on the coagulation system, an antioxidant system, and hepatic and lipoprotein lipase activities. Moreover, plant sterols have been shown to have other metabolic effects. For example, several epidemiological and animal studies suggest that phytosterols suppress the growth of colon tumors.

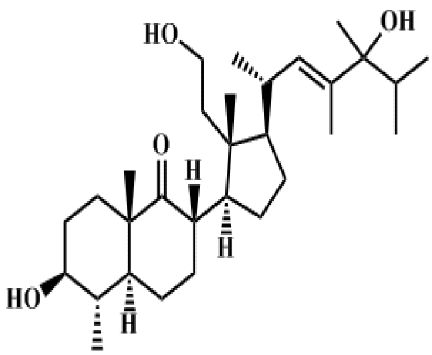
Humans are not able to synthesize phytosterols, and dietary consumption is the only source of these compounds. Thus, human intake of phytosterols is governed by eating habits and the availability of the source of plant sterols.

Lepidium sativum contained the highest number of sterols. Among them, γ-sitosterol (12.2%) and ergost-5-en-3-ol (3β) (4.5%) were found to be the major constituents. Moreover, three of the identified molecules [stigmasta-5,23-dien-3β-ol, stigmasta-5,24(28)-dien-3-ol (3β,22E) and 9,19-cyclolanost-24-en-3-ol (3γ)] were found in this plant only.

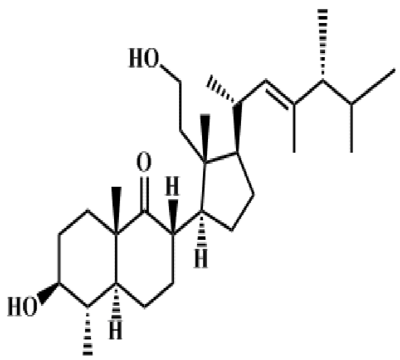
Strong anti-inflammatory activity was detected in *Picris hieracioides*, *Foenicum vulgare, Cichorium intybus* leaves and *Cynara cardunculus*, *P. hieracioides* contained only γ-sitosterol. γ-Sitosterol and stigmasterol were the predominant sterols since they were widely distributed. The first one was identified in every plant, exception *Foenicum vulgare* and it was mainly contained in *Lepidium sativum* , *Cichorium intybus* leaves and *Sonchus oleraceus* (12.2%, 9.5% and 6.5%, respectively).

Stigmasterol was identified in extracts. The amount was particularly high for *Cichorium intybus* extracts (4.3% in root extract and 3.6% in leaves). Ergost-5-en-3-ol (3β) and campesterol were less widely distributed.[29]

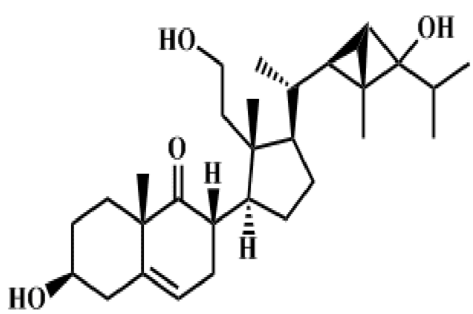
Marine invertebrates have proven to be a prolific producer of novel sterols; relatively few secosterols have been isolated so far. For the several examples of the known secosterols, only in vitro cytotoxicity has been reported. Secosterols 1-3, 6 and 7 which isolated from *Gorgonian Pseudopterogorgia sp*.exhibited moderate inhibitory activity against protein kinase C, and 6 showed potent antiproliferative and anti-inflammatory activity.[30]



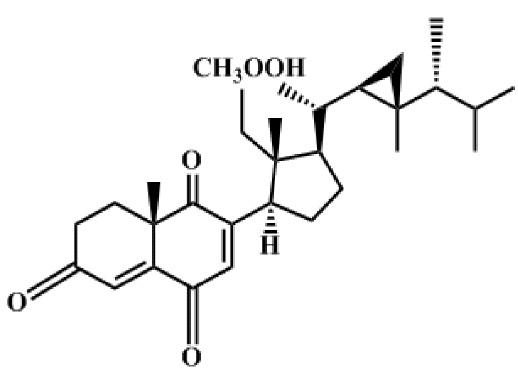
Secosterol-1



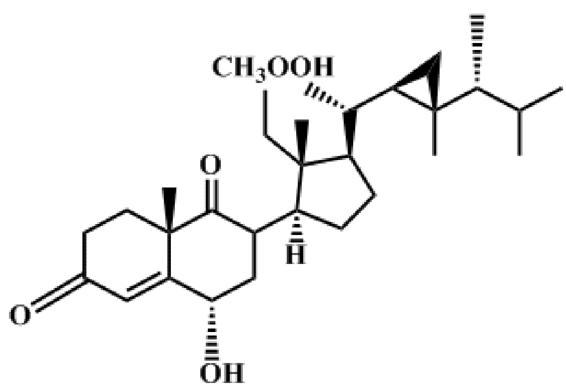
Secosterol-2



Secosterol-3



Secosterol-6



Secosterol-7

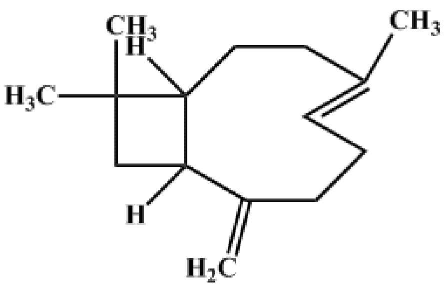
Figure-8: 9,11-Secosterols from *Pseudopterogorgia* sp.

Terpenoids and Essential oils

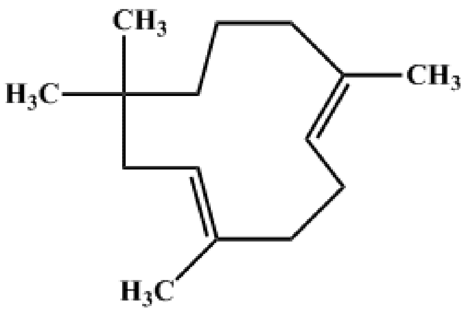
Essential oils are volatile, natural, complex compounds characterized by a strong odour and are formed by aromatic plants as secondary metabolites. Essential oils are highly enriched in compounds based on an isoprene structure. They are called terpenes, their general chemical structure is $C_{10}H_{16}$, and they occur as diterpenes, triterpenes, and tetraterpenes (C_{20}, C_{30}, and C_{40}), as well as hemiterpenes (C_5) and sesquiterpenes (C_{15}). When the compounds contain additional elements, usually oxygen, they are termed terpenoids. Examples of common terpenoids are menthol and camphor (monoterpenes) and farnesol and artemisin (sesquiterpenoids). Artemisin and its derivative∝-arteether, also known by the name qinghaosu, find current use as antimalarials.

Above mentioned compounds possesses antiseptic activity, i.e. bactericidal, virucidal and fungicidal and they are also used in embalment, preservation of foods and as antimicrobial, analgesic, sedative, anti-inflammatory, spasmolytic and locally anesthesic remedies.[31] It is often quite difficult to compare the results obtained from different studies, because the compositions of the essential oils can vary greatly depending upon the geographical region, the variety, age of the plant, the method of drying and the method of extraction of the oil. In recent years, several researchers have reported that mono-and sesquiterpene hydrocarbons and their oxygenated derivatives as the major components of essential oils of plant origin, which have potent anti-inflammatory effect.[32]

The analgesic and anti-inflammatory effects of the essential oils of many species of the genus *Eucalyptus* (Myrtaceae)[33], *Cordia verbenacea* (Boraginaceae)[34], *Lippia sidoides* leaves (Verbenaceae)[35], *Lippia gracilis* Schauer leaves (Verbenaceae), and *Zizyphus jujube* seed[32] were established.



Trans-caryophyllene



α-humulene

Figure 9: Essential oil from *Cordia verbenacea*

Conclusion

Much research has shown that secondary compounds, present in various plants exert beneficial effects on human health such as cardiovascular protection, anti-cancer activity, anti nociceptive activity as well as anti inflammatory effects.

The public is becoming increasingly aware of problems with the over prescription and misuse of synthetic anti-inflammatory drugs. Many people are now days interested in the treatment of inflammation by plant compounds and many herbal preparations are available over-the-counter from herbal suppliers and natural-food stores, and self-medication with these substances is commonplace.

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