



ELSEVIER



 Clinics in
 Dermatology

1
2 **Original article**

3 **The internal and external use of medicinal plants**

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6 **Introduction**

7
8 There is a growing trend in skin care to use those materials
9 that have had success in the growing dietary supplement
10 preparations. The justification for using a plant, herb, or
11 spice externally based on its internal therapeutic value bears
12 no logic at all scientifically, and yet with surprising regularity
13 there is justification for this way of thinking although
14 sometimes the effects are in no way related.

15 **Cautionary warnings in the UK**

16 The term *cosmeceuticals* should be used with caution, as
17 there are separate pieces of legislation that apply to pharma-
18 ceutical and cosmetics in the United Kingdom, which have
19 corresponding legislation that applies to the European Union.

20 The manufacture of cosmetics and toiletries is more
21 regulated than the food industry but not to the extent of the
22 pharmaceutical industry. The comparison between the
23 production of pharmaceuticals in terms of good manufactur-
24 ing practice and the cosmetics and toiletries industry is not
25 that dissimilar.

26 In Europe, the USA, and Japan, the laws are quite specific
27 and although these three strive to achieve parity, there are
28 still many differences between the various legislative
29 documents, particularly in the area of sun care, antiperspir-
30 ants, and toothpaste.

31 The EEC has Council Directive 76/768/EEC up to the
32 27th amending Directive 2003/15/EC and including the
33 previous 26 amendments and this has to be translated into the
34 language of each member state; in the UK the law is

35 Statutory Instrument 2004 No. 2152 The Cosmetic Products
36 (Safety) Regulations 2004. A Commission decision 9
37 February 2006 amended Decision 96/335/EC and estab-
38 lished an (updated) inventory and a common nomenclature
39 of ingredients used in cosmetic products (2006/257/EC).
40 This is a most useful document for correct product labeling.

41 In addition, products must not infringe the Medicines for
42 Human Use (Marketing Authorisations Etc) Regulations
43 1994, a very common infringement with today's eagerness
44 to have "alluring" pack copy. The Regulations provide that,
45 unless exempt, any "medicinal product" to which Chapters II
46 to V of Directive 2001/83/EEC apply must not be placed on the
47 UK market unless it has a marketing authorization (product
48 license) granted by the European Commission or by the UK
49 Licensing Authority. The Act similarly provides that, unless
50 exempt, any other "medicinal product" must not be sold or
51 supplied without a marketing authority. A marketing author-
52 ization or product license is only granted for a product which
53 meets statutory standards of safety, quality, and efficacy.

54 The status of many products on the "borderline" between
55 medicinal products and food supplements, cosmetic or
56 medical devices can be difficult to determine. The Medicine
57 and Healthcare products Regulatory Agency have produced
58 a Guidance Note 8 document to explain how and on what
59 basis the MCA decides whether products are medicines or
60 not. It includes guidance on the statutory procedures in
61 Regulation 3A of the Regulations introduced by the
62 Medicines for Human Use (Marketing Authorisations Etc)
63 Amendment Regulations 2000 (SI 2000/292).

64 There is also the requirement to ensure that claims made
65 on the packaging comply with the Trade Descriptions Act
66 1968, Control of Misleading Advertising Regulations 1988
67 (as amended). Products must also comply with the Weights
68 and Measures Act 1985.

69 Certain categories (eg, insect repellants and products that
70 contain this property) may also be subject to the Statutory

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71 Instrument 2003 No. 429 The Biocidal Products (Amend-
72 ment) Regulations 2003.

73 Compliance with these laws is mandatory in Europe and
74 many countries have adopted them with little alteration. It
75 will be the way of things to come and most countries are in
76 the process of harmonizing and adopting these legal
77 safeguards. Any company that does not react ahead of the
78 inevitable is going to find it an arduous and almost
79 impossible task to implement in the time frames that are
80 normally allowed for full compliance.

81 Definition of natural

82 It is a curious fact, but there are no legal definitions of
83 natural and this provides much subject for debate and
84 litigation as law enforcement agencies argue interpretation
85 with marketers of products placed onto the market.

86 We would define natural as any material that is harvested,
87 mined, or collected, and which may have subsequently been
88 washed, decolorized, distilled, fractionated, ground, milled,
89 separated, or concentrated to leave a chemical or chemicals
90 that would be available and detectable in the original source
91 material. It is also the modification of natural material by the
92 action of microorganisms, enzymes, or yeasts to modify or
93 increase the yield of material by this process.

94 Naturally derived materials are defined by the use of a
95 natural raw material as the starting point in a chemical
96 process to produce a new chemical or chemicals that in
97 themselves may not be available in nature or in the starting
98 material.

99 Nature identical material is a substance that has been
100 produced synthetically, not usually from a natural starting
101 material, to produce a material that is identical to that
102 naturally occurring in nature.

103 Sources of data for products that may have 104 topical "cosmeceutical benefit"

105 There are many ethnopharmaceutical applications for
106 topical application that have been used for countless
107 generations and that are tried and tested in those countries
108 where their use is prevalent. In many cases, these are well
109 described in the literature and have been identified from their
110 phytochemical composition, preparation, part used, and
111 dosage. This search is no longer restricted to the European
112 systems of herbal medicine but now extends to Russian,
113 Chinese, Indian system of Ayurvedic and Unani, African,
114 and, more recently, Aboriginal traditional medicine.

115 Less reliable sources are the "Grandmother's recipe" or
116 folk lore, which passes from generation to generation
117 without any real scientific study or analysis. The works of

the old herbalists like Galen, Dioscorides, Culpeper, 118
Hildegard von Bingen, and Paracelsus (Theophrastus 119
Bombastus von Hohenheim) may give some insights to future 120
investigation. In some cases, these remedies may be 121
discounted after serious evaluation, but there are still many 122
occasions when science substantiates their beneficial use. 123

Plants are complex chemical factories 124

A plant is a complex and ever active chemical factory that 125
produces a wide range of chemical moieties that it requires 126
for protection against yeast and moulds, resistance to insect 127
attack, even the protection against ultraviolet and drought 128
conditions in some specialist plants. Other coastal region 129
plants require very specific protection against salts and 130
excess minerals. It is this complex environment that produces 131
many dozens of chemical entities that may have benefit in 132
human treatments for various skin conditions. 133

The composition may vary according to the area of 134
growth (country), the soil, the weather conditions, the time of 135
harvest, the processing, and of course the part of the plant 136
that is being extracted. The storage conditions of the plant, 137
the time of extraction, and the solvents used in that extraction 138
will all have a significant implication on the final chemical 139
composition, for example, the content of natural preserva- 140
tives produced by plants to protect the fruit and the leaves 141
will fall dramatically once they have been separated from the 142
main plant. This can be easily demonstrated by smelling a 143
fresh bloom on a living rose and then cutting off that flower. 144
In a matter of minutes, the rose note will alter drastically as 145
the chemical composition alters. 146

The pharmaceutical industry and the purists would 147
always prefer to work with single chemical entities derived 148
from a single plant. Although this sounds a perfect solution 149
for reproducibility, the truth is very different. Plants tend to 150
have a full orchestra of individual phytochemically active 151
materials that work synergistically in harmony. The overall 152
result is that the effect of the individual components is far 153
outweighed by the blend. In Traditional Chinese Medicine, 154
the normal herbal treatment is tailored for an individual and 155
targets both underlying causes and their effects. In the Far 156
East, they recognize that in some seasons a particular plant 157
may lack potency but that another plant attributed with 158
having the same effect is substantially rich and effective, 159
that is, one plant thrives in a rainy season but suffers in a 160
hot dry season and vice versa. Blends that involve 8 or 161
more herbal materials is not uncommon with each pair 162
acting on different indications, like pruritis, erythema, 163
edema, circulation, granulation, re-epithelialization, and 164
cicatratization. Although the terminology used in Traditional 165
Chinese Medicine may seem strange to Westerners, the 166
correlation to terms we do understand and theirs is an 167
almost perfect match. 168

169 Fatty acids

170 The simplest treatment of dry skin conditions is with fixed
171 vegetable oils. Many of these vegetable, nut, seed, and kernel
172 oils are simple blends of fatty acids with varying carbon
173 chain lengths. Coconut, sunflower, safflower, rapeseed, corn,
174 or sesame seed oil will give perfectly acceptable skin
175 coverage and are most often used as carrier oils for essential
176 oils. These oils will coat the skin, to occlude and protect it by
177 slowing down transepidermal water loss and so increasing
178 hydration within the stratum corneum and top layers of the
179 dermis. They will also “glue down” dry and desquamated
180 skin cells to make the skin look less rough and scaly.

181 Some oils like castor seed oil (*Ricinus communis*) are
182 renowned not only for their very high gloss (and so a
183 frequent component in lipsticks and lip salves), but also for
184 their high degree of occlusiveness which makes them ideal
185 for skin protection, for example, diaper or nappy rash
186 creams, where the most traditional and best known example
187 would be zinc and castor oil cream.

188 Other oils like evening primrose oil (*Oenothera biennis*),
189 borage (aka starflower), seed oil (*Borago officinalis*), and
190 blackcurrant seed oil (*Ribes nigrum*) are particularly useful
191 because of their high γ -linolenic acid content. Evening
192 primrose used to hold a pharmaceutical license for use on
193 atopic dermatitis, but subsequently lost this status on the
194 publication of further clinical trial data. It is still widely taken
195 orally for mastitis (breast pain).

196 A new oil made commercially available in 2006 is Inchi oil
197 (*Plukenetia volubilis*) which also has the name Aztec peanut—
198 although it is totally unrelated to the peanut (*Arachis*
199 *hypogaea*). This oil is abundant in ω -3, ω -6, and ω -12 fatty
200 acids, and could well show huge promise in skin care.

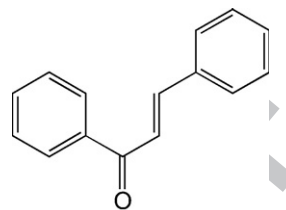
201 Another that is rich in γ -linolenic acid is a particular
202 species of rose hip seed oil (*Rosa aff rubiginosa*) that is
203 collected in the foothills of the Chilean Andes and often
204 called *Rosa moschata*. This oil is reputed to contain vitamin
205 A according to some references. A large body of evidence
206 (mainly anecdotal clinical) suggests that this oil has
207 exceptional cicatrizing properties and is an excellent oil for
208 restoring skin elasticity especially for postsurgical conditions
209 where tightness has become a problem for the patient. It was
210 also shown to be effective for treating the hyperpigmentation
211 of certain scar tissue.

212 Flavonoids

213 *Flava* means yellow in Greek and the collective name of
214 flavonoids for this group of compounds was proposed by
215 Geissman in 1952. This is a very large group of compounds
216 showing extraordinary diversity and variation and as the
217 Greek root for the group suggests, as many of these
218 compounds are yellow in color.

219 They consist of a number of structurally related groups of
220 products, which are often identified as polyphenols. Many

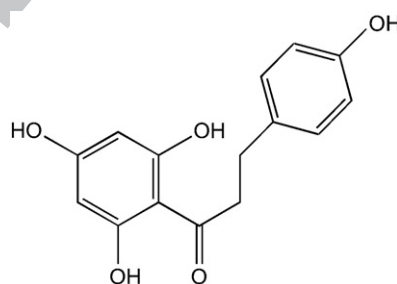
221 have a basic skeleton that contains 15 carbon atoms, which
222 are usually subdivided into one part made up from a phenolic
223 (C6) moiety and another which has a cinnamic acid molecule
224 (C13) as a building block. The group called the **chalcones**
225 may be considered as the Friedel-Crafts reaction product of a
226 (substituted) cinnamic acid and a phenol.



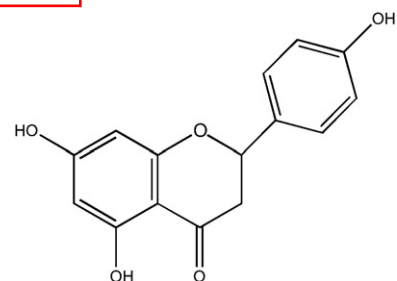
228 **Fig. 1** Example of chalcone structure.

229 Flavonoids may be found as their glycosides. These are
230 molecules that are substituted on one or more of the hydroxyl
231 groups with a sugar such as galactose, glucose, mannose, or
232 rhamnose, etc. The aglycons do not carry a sugar moiety.

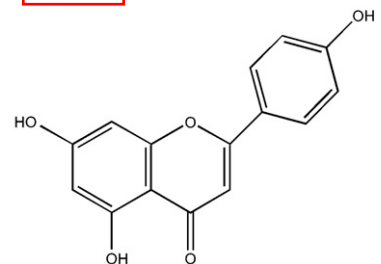
233 Reductive ring closure of chalcones results in the
234 formation of a flavone. **Naringenin chalcone** is converted
235 to **naringenin** by ring closure, from which **apigenin** (4',5,7-
236 trihydroxyflavone) is then formed.



238 **Fig. 2** Naringenin chalcone.



239 **Fig. 3** Naringenin.



242 **Fig. 4** Apigenin.

Flavones are generally found in herbaceous families such as Labiatae, Umbelliferae, and Compositae. Important flavones are apigenin (*Apium graveolens* [celery], *Carum petroselinum* [parsley]; 4',5,7-trihydroxyflavone), luteolin (*Equisetum arvense* [horsetail] 3',4',5,7-tetrahydroxyflavone), and diosmetin (3',5,7-trihydroxy-4'-methoxyflavone). Many flavones occur as glycosides. Flavones also occur in nature in association with tannins (polyesters of gallic acid; 3,4,5-trihydroxybenzoic acid). Gallic acid and its esters (eg, propyl gallate, dodecyl gallate) are well known as powerful antioxidants, and, probably, these products fulfill a similar role in higher plants.

Next to the *O*-glycosides, flavones also occur as *C*-glycosides. This has not been reported for other flavonoids. Examples of *O*-glycosides are vitexin (3,4',5-trihydroxy-2-glucosylflavone) and isovitexin (3,4',5-trihydroxy-4-glucosylflavone).

The simplest representative of the group of flavones is "flavone," which does not carry any hydroxy, methoxy, or glycosidic groups. It naturally occurs as "dust" on flowers and leaves.

An interesting synthesis of flavones is by ring expansion of 2-benzylidenecoumaran-3-ones (Wheeler). These substances are known as aurones, and several have been reported to occur naturally. In aurones, the 6-membered heterocyclic ring is replaced by a 5-membered ring. An example of an aurone is sulfuretin, 6,3',4'-trihydroxyaurone.

Flavones with a hydroxy group on the 3-position (3-hydroxyflavones) are usually considered as a separate group and are named flavonols. To this group belongs the most important product **quercetin** (3,3',4',5,7-pentahydroxyflavone). An important commercial source for quercetin is the glycoside quercetin, which is present in large amounts in the bark of *Quercus tinctoria*.

Quercetin is also present in significant concentration in *Ruta graveolens* (rue), *Fagopyrum esculentum*, and *Sambucus nigra* (elder flower). Quercetin is a very potent phosphodiesterase inhibitor with significant application potential. Quercetin is probably the most frequently occurring botanical pigment, and many glycosides of quercetin have been isolated and identified.

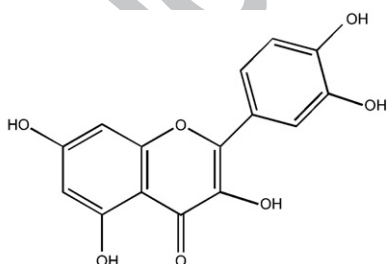


Fig. 5 Quercetin.

The flavonols **kaempferol** (3,5,7,4'-tetrahydroxyflavone; present in *S. nigra*, *Cassia senna*, *E. arvense*, *Lamium album* [white nettle], and *Polygonum bistorta*) and Myricetin (3,5,7-trihydroxy-3',4',5'-trimethoxyflavon; occurs in *Gly-*

cyrrhiza glabra [licorice]) occur in many botanical extracts to which they give a significant value added.

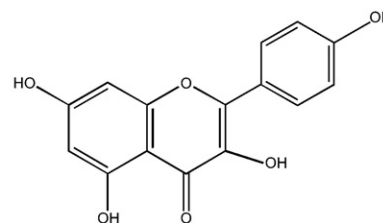


Fig. 6 Kaempferol.

Other interesting flavonols are galangin (3,5,7-trihydroxyflavone; galanga root) and gossypetin (gossypol; 3,5,7,8,3',4'-hexamethylflavone; occurs in *Gossypium herbaceum* [cotton]). Gossypetin has anticarcinogenic, antiviral, and anti-allergic activity, and is active against infections with Trypanosomes, fisetin, and rhamnetin.

Isoflavones

Isoflavones have the phenyl group attached to the 3-position, whereas in flavones the phenyl group is attached to the 2-position. The isoflavones are mainly found to occur within the Leguminosae (specifically in the subfamily Papilionoideae), although the literature shows many other species that contain these chemical moieties.¹ Isoflavones are also found in other botanical families such as the Compositae, the Iridaceae, the Myricaceae, and the Rosaceae.

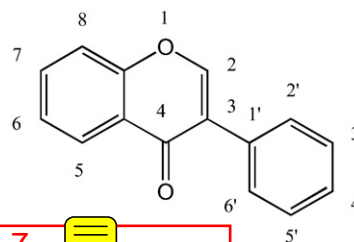


Fig. 7

These isoflavones can act as steroidal mimics by filling the stereochemical space that could be occupied by estrogenic compounds. It is this special chemistry that helps explain the effects of many nutritional herbal supplements and topical preparations.

Daidzein is a phytoestrogen, but is also called a phenolic estrogen, to distinguish it from a steroidal estrogen like 17 β -estradiol (Figs. 1 and 2). The activity of phytoestrogen is much weaker than the steroidal estrogen, varying from 0.005% to 2%.³ The estrogenic properties are insufficient in strength to replace steroidal estrogens, but they do have significant value when it comes to reducing the effects of ageing and improving the quality of the skin.

Phytoestrogens may also be viewed in relation to the phytochemical division of terpenoids, which comprise the largest group of natural plant products. All terpenoids are derived biogenetically from isoprene. The largest group of

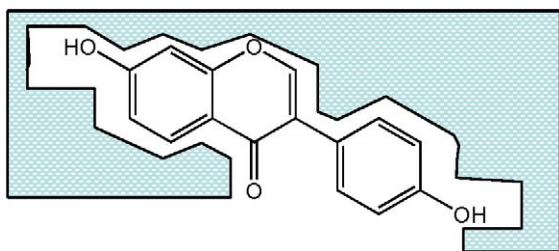


Fig. 8 Estrogen receptor with daidzen.

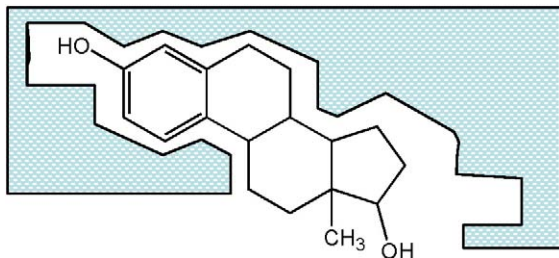


Fig. 9 Estrogen receptor with 17β-estradiol.

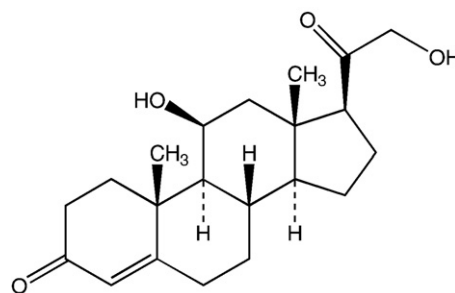


Fig. 12 Corticosterone.

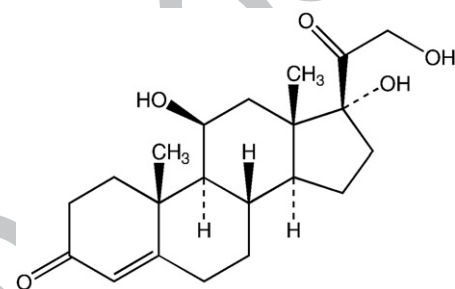


Fig. 13 Hydrocortisone.

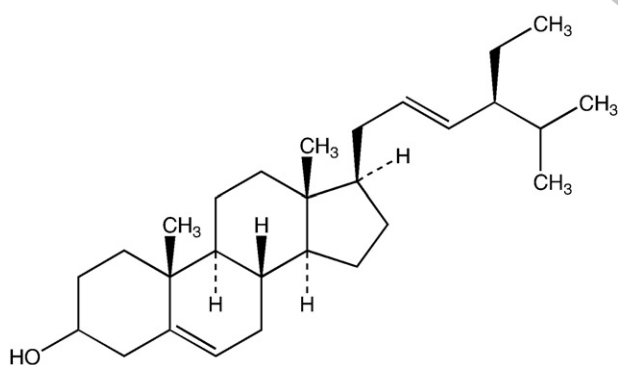


Fig. 10 Stigmasterol.

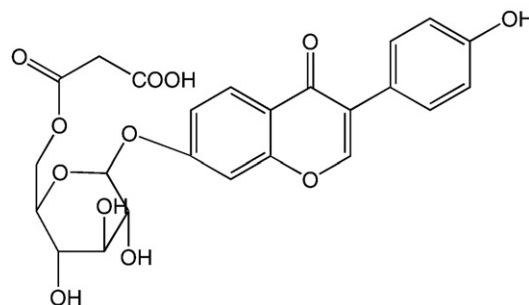


Fig. 14 Malonyldaidzin.

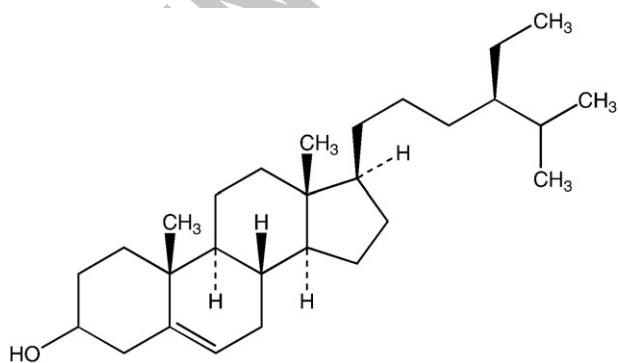


Fig. 11 β-Sitosterol.

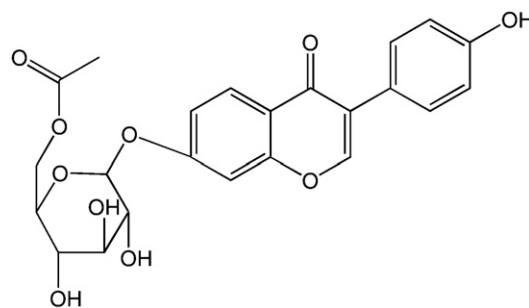


Fig. 15 Acetyldaidzin.

329 terpenoids is the triterpenoids, which include, among other
330 divisions, the triterpenoid and steroid saponins, and, the
331 phytosterols. The phytoestrogens fall into these 3 categories.

332 In addition, nature has a rich portfolio of phytosterols. It is
333 easy to understand why sterols like stigmasterol (Fig. 3) and
334 β -sitosterol (Fig. 4) have an effect that is anti-inflammatory
335 and capable of reducing swelling and erythema, when their
336 structure is compared to corticosterone (Fig. 5) and
337 hydrocortisone (Fig. 6).

The most commonly occurring isoflavones are

| | |
|----------------------------------|------------------------------------|
| Biochanin-A | 5,7-dihydroxy-4'-methoxyisoflavone |
| Daidzein | 4',7-dihydroxyisoflavone |
| (+/-)-Equol | 4',7-isoflavandiol |
| Formononetin | 7-hydroxy-4'-methoxyisoflavone |
| Glycitein | 4',7-dihydroxy-6-methoxyisoflavone |
| Genistein | 4',5,7-trihydroxyisoflavone |
| Genistein-4', 7-dimethylether | 5-hydroxy-4',7-dimethoxyisoflavone |
| Prunetin | 4',5-dihydroxy-7-methoxyisoflavone |

with the associated glucosides

| | |
|-----------|--|
| Genistin | glucosyl-7-genistein |
| Glycitin | 4',7-dihydroxy-6-methoxyisoflavone-7-d-glucoside |
| Ononin | formononetin-7-O-glucoside |
| Sissotrin | Biochanin A-7-glucoside |

Daidzein

353 Daidzein is a solid substance that is virtually insoluble in
354 water. Its molecular formula is $C_{15}H_{10}O_4$, and its molecular
355 weight is 254.24 da. Daidzein is also known as 7-hydroxy-3-
356 (4-hydroxyphenyl)-4H-1-benzopyran-4-one and 4',7-dihy-
357 droxyisoflavone. Daidzin, which has greater water solubility
358 than daidzein, is the 7- β glucoside of daidzein.

359 Daidzein is an isoflavone. It is also classified as a
360 phytoestrogen as it is a plant-derived nonsteroidal compound
361 that has estrogen-like biological activity. Daidzein is the
362 aglycone (sometimes called the aglucon) of daidzin (see

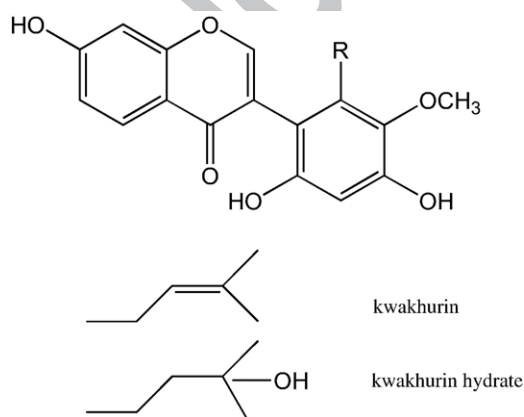


Fig. 16 Kwakhurin, kwakhurin hydrate.

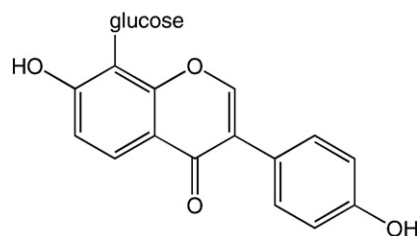


Fig. 17 Puerarin.

363 Fig. 1). The isoflavone is found naturally as the glycoside
364 daidzin and as the glycosides 6''-O-malonyldaidzin (Fig. 7)
365 and 6''-O-acetyldaidzin (Fig. 8). Daidzein and its glycosides
366 are mainly found in the Leguminosae family that includes
367 soy beans and chickpeas.

368 Soybeans and soy foods are the major dietary sources of
369 these substances. Daidzein glycosides are the second most
370 abundant isoflavones in soybeans and soy foods; genistein
371 glycosides are the most abundant.

372 Nonfermented soy foods, such as tofu, contain daidzein,
373 principally in its glycoside forms. Fermented soy foods, such
374 as tempeh and miso, contain significant levels of the aglycone.

Kudzu vine (*Pueraria labata*)

375 The roots of *P labata* is an herbal medicine commonly
376 known as the kudzu vine. It has been used for centuries in
377 traditional Chinese medicine for the treatment of alcohol
378 abuse and thought to be effective because of the daidzein and
379 daidzin found in the herb. A study on Syrian Golden
380 Hamsters suppressed the alcohol choice.²⁰
381

White kwao kua (*Pueraria mirifica*)

382 In addition to genistein, daidzein (see above), daidzin, and
383 genistin, the plant contains a some unique isoflavones, kwak-
384 hurin, kwakhurin hydrate (Fig. 9), and puerarin (Fig. 10),
385 to name but a few.¹³
386

387 The roots also contain mirificoumestan (Fig. 11), deoxy-
388 miroestrol (Fig. 12), and coumestrol (Fig. 13). The
389 traditional use of the plant is clearly for the hormonal
390 properties, as in Thailand it is used for breast development.

391 When *P mirifica* is taken as a dietary supplement, its
392 phytoestrogen constituents will naturally alleviate symptoms

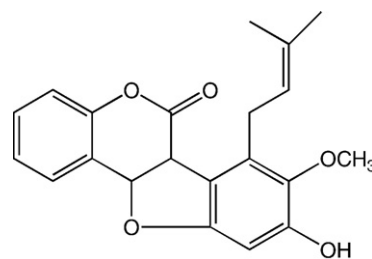


Fig. 18 Mirificoumestan.

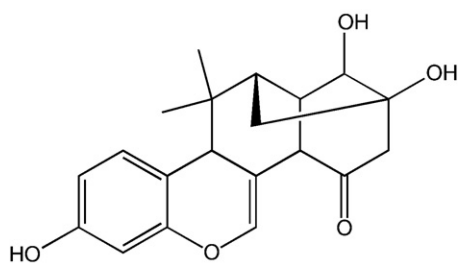


Fig. 19 Deoxymiroestrol.

393 occurring as a result of the aging process and a deficiency in
394 estrogen levels, for example, sagging breasts, wrinkled skin,
395 bone loss, gray hair, etc. These aging signs and symptoms
396 will, to a certain extent, be reversed.

397 The rich source of sterols and phyto-hormones also
398 indicates the plant for the topical treatment of wrinkles and
399 aging skin conditions.

400 Red clover (*Trifolium pratense* L) 401 (Leguminosae)

402 The flowerheads are used and they contain the following
403 isoflavones: biochanin A, daidzein, formononetin, genistein,
404 pratensein, and trifoside. The plant has alterative, antispas-
405 modic, and expectorant properties, and is a sedative
406 dermatologic agent. Its main use is an alterative and for
407 skin complaints such as psoriasis and eczema, as well as an
408 expectorant use in coughs and bronchial conditions.^{37,38}

409 Biochanin A (Fig. 14) and formononetin (Fig. 15) are 2
410 isoflavones from red clover and are just like genistein and
411 daidzein, except that they have methyl groups replacing the
412 hydroxyl groups.

413 These 2 isoflavones are considerably less estrogenic in
414 their original forms, because the stereochemistry of the
415 methoxy groups means they are not able to bind to the
416 estrogen receptors as efficiently.

417 However, once these molecules are ingested, bacteria in
418 the colon are able to remove the methyl groups—biochanin
419 A becomes genistein (Fig. 16) and formononetin becomes
420 daidzein (Fig. 1 see above). Daidzein can be further
421 metabolized to equol (Fig. 17).

422 Internally, biochanin A and formononetin are then able to
423 be a source of considerable estrogenic activity.

424 It may well be that these mechanisms give red clover its
425 reputation as an alterative remedy, cleansing the system yet
426 mild enough for many children's skin problems, even

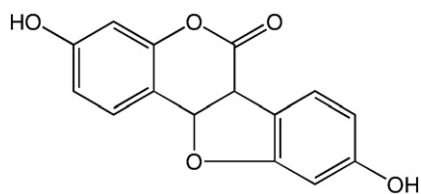


Fig. 20 Coumestrol.

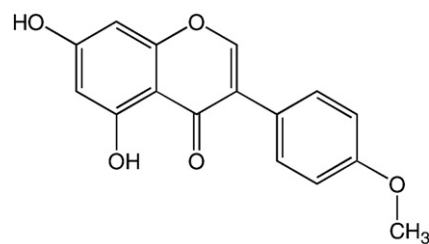


Fig. 21 Biochanin A.

427 eczema. A lotion of red clover can be used externally to
428 give relief from itching in skin disorders. Specific for acne,
429 boils, and similar eruptions, including eczema and skin
430 problems especially where irritation is a factor.¹⁴

431 Historically, the flower tea has been used as an
432 antispasmodic, expectorant, and mild sedative. It is also
433 recommended for athlete's foot, sores, burns, and ulcers,²³
434 and has been used in the herbal treatment of cancer,
435 especially of the breast or ovaries.²⁶

436 Red clover is also a very popular remedy as the alternative
437 for hormone replacement therapy and is sold extensively for
438 this purpose.

439 Sweet yellow melilot (*Melilotus officinalis*)

440 Melilot is soothing, lenitive, astringent, refreshing, and
441 anti-irritant, and has similar properties to the red clover
442 described above. It is also described as possibly having the
443 additional properties of being anti-inflammatory, anti-edema,
444 a venous astringent (hemorrhoids), and anesthetic.⁹

445 It is perhaps not the isoflavones at force here, however,
446 but may be the β -sitosterol or coumarin the roots contain.

447 *Melilotus officinalis* L extract, containing 0.25% cou-
448 marin (Fig. 18), was studied on acute inflammation induced
449 with oil of turpentine in male rabbits. *M. officinalis* had anti-
450 inflammatory effects because it reduced the activation of
451 circulating phagocytes and lowered citrulline production.

452 These properties were similar to those of hydrocortisone
453 sodium hemisuccinate and coumarin.³¹

454 Phytosterols and related compounds

455 The benefits of these phytosterols may be seen in the
456 common herbal materials indicated for arthritis, such as
457 Frankincense (*Boswellia serrata*). The boswellic acid

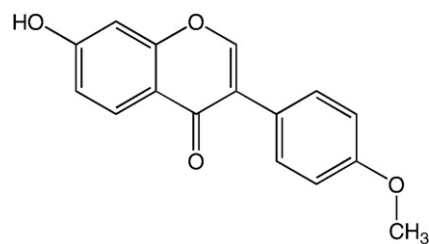


Fig. 22 Formononetin.

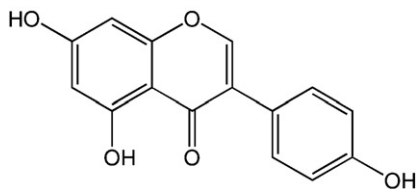


Fig. 23 Genistein.

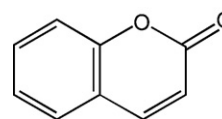


Fig. 25 Coumarin.

Q4 458 (Fig. 19) present inhibits 2 inflammatory enzymes, 5-
459 lipoxygenase (which produces leukotrienes) and human
460 leukocyte elastase HLE (which degrades elastase).

Q5 461 The Committee on Toxicity of Chemicals in Food,
462 Consumer Products and the Environment, Working Group
463 on Phytoestrogens Cellular and Molecular Mechanisms of
464 Phytoestrogen Activity.

465 The Department of Biochemical Pharmacology, Imperial
466 College School of Medicine prepared a paper for discussion:
467 "Assessment of the estrogenic potency of phyto-com-
468 pounds". This reviewed the available information on cellular
469 and molecular mechanisms and phytoestrogen estrogenic
470 potencies. Of the 28 points (statements for comment really)
471 the following stood out.

472 Taking all estrogen receptor binding assays into account the
473 review proposed the following rank order of phytoestrogen
474 potency: estradiol \gg coumestrol > 8-prenylnaringenin > equol
475 \gg genistein > biochanin A > daidzein > genistein
476 glucuronide* > daidzein glucuronide* > formononetin (the
477 activity of those compounds marked * may be due to the pre-
478 sence of activating enzymes present in the receptor preparation).

479 Phytoestrogens stimulated in vitro cell proliferation at
480 concentrations of 0.1 to 10 mmol/L (3- to 4-fold less than
481 estradiol). They did not induce the maximal proliferative effect
482 of estradiol as higher concentrations inhibited proliferation.

483 The majority of endogenous estrogens (>90%) were not
484 freely available but bound to plasma proteins. Phytoestrogens
485 bound at 1/100th to 1/1000th the affinity of estradiol.
486 The availability of phytoestrogens in plasma relative to
487 estradiol will be greater.

488 Coumestrol, 8-prenylnaringenin, and equol were more
489 than 1000-fold less potent than estradiol and the isoflavones
490 were more than 10 000-fold less potent.

491 The wild yam (*Dioscorea villosa*)

492 The wild yam (*D villosa*) was the source of diosgenin
493 (Fig. 20), a steroidal saponin used as the starting point for the

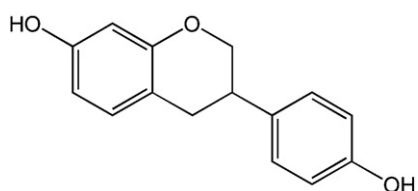


Fig. 24 Equol.

commercial source of pregnanolone (Fig. 21) and progester-
one (Fig. 22) used as the first birth control pills. The root of
Dioscorea is used for numerous purposes, but the major use
is for the suppression of menopausal symptoms like hot
flushes.³⁵

There are many other sources of diosgenin.

During pregnancy, small frequent doses will help allay
nausea^{16,24,25}. It is antispasmodic. It is valuable neuralgic
affections, spasmodic hiccough, and spasmodic asthma.¹⁶

It is spasmolytic, a mild diaphoretic. It has potential in
skin care and body care being anti-inflammatory and anti-
rheumatic.

It is also cited for dysmenorrhea, ovarian, and uterine
pain,^{4,17} perhaps showing the power of this herbal root.

It is interesting to note that *Vitex agnus-castus* is a source
of natural progesterone. Proprietary preparations containing
this material have been available in Germany since the 1950s
and many documented studies have investigated the use of
these products to treat various gynecologic disorders.²⁷ The
fruit of *Vitex* contains essential oils, iridoid glycosides, and
flavonoids. Essential oils include limonene, 1,8 cineole, and
sabinene.³ The primary flavonoids include castican, orientin,
and isovitexin. The 2 iridoidglycosides isolated are agnuside
and aucubin. Agnuside serves as a reference material for
quality control in the manufacture of *Vitex* extracts. One
other report demonstrated δ -3-ketosteroids in the flowers and
leaves of *Vitex* that probably contained progesterone and 17-
hydroxyprogesterone.⁵ The active constituents have been
determined as 17- α -hydroxyprogesterone (leaf), 17-hydroxy-
progesterone (leaf), androstenedione (leaf), δ -3-ketoster-
oids (leaf), epitestosterone (flower), progesterone (leaf),
testosterone (flower and leaf).³⁰

It is highly unlikely that the diosgenin in the plant could
ever be synthesized on the topical application to the skin to
form a corticosteroid or hormonal derivative. It does seem
likely, however, that this material (being the precursor to
these estrogenic molecules) will, to some extent, mimic the

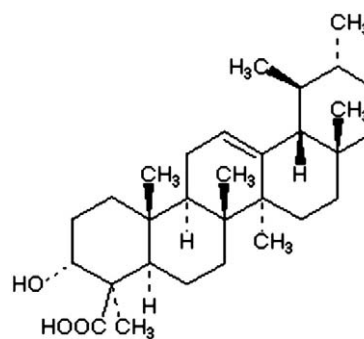


Fig. 26 Boswellic acid.

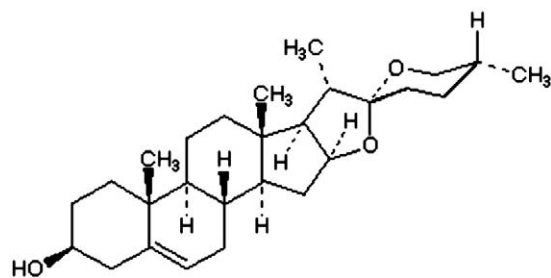


Fig. 27 Diosgenin.

531 function of those pharmaceutical active materials and benefit
532 the skin.¹²

533 The production of wild yam, however, was unable to
534 sustain the demand for diosgenin as the starting precursor, for
535 the production of birth control materials, which by this stage
536 was dominated by estrone (Fig. 23).

537 Fenugreek (*Trigonella foenum graecum*)

538 The world turned its attention to fenugreek (*T foenum*
539 *graecum*) for its source of diosgenin.

540 Fenugreek or foenugreek seeds are emollient and
541 accelerate the healing of suppurations and inflammations.
542 Externally cooked with water into a porridge and used as hot
543 compresses on boils and abscesses in a similar manner to the
544 use of linseed.¹⁵

545 Decoctions of whole plant are used as a bath for uterus
546 infections. The seeds are tonic, restorative, aphrodisiac, and
547 galactagogue. Their emollient properties are useful for the
548 itch. A cataplasm obtained by boiling the flour of the seeds
549 with vinegar and saltpeter is used for swelling of the spleen.²
550 Extracts of the seeds are incorporated into several cosmetics
551 claimed to have effect on premature hair loss, and as a skin
552 cleanser,¹⁹ and it is also reported in Java in hair tonics and to
553 cure baldness.²² Many of the herbal materials found to have
554 an effect on hair growth have a hormonal or hormonal-
555 mimetic basis.

556 Likewise, there are a number of references to fenugreek
557 having galactagogue (increase milk in nursing mothers)
558 activity,^{6,7,26} which again is indicative of an estrogen-like
559 activity. The plant should be used with caution as fenugreek
560 is reputed to be oxytocic and in vitro uterine stimulant

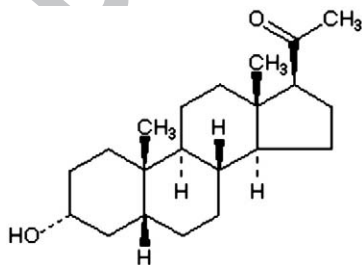


Fig. 28 Pregnanolone.

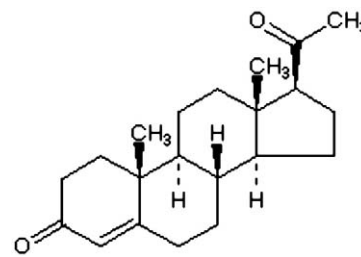


Fig. 29 Progesterone.

561 activity has been documented,²⁷ so the use of fenugreek
562 during pregnancy and lactation in doses greatly exceeding
563 those normally encountered in foods is not advisable.

564 Pomegranate (*Punica granatum*)

565 Pomegranate is one of the many plants that contain
566 substances with hormone-type action. The seeds of pome-
567 granate, that ancient symbol of fertility, were found to
568 contain an estrone identical with the genuine hormone. *Pu-*
569 *nica granatum* seeds are the best source of plant estrone to
570 date.³⁶

571 The antioxidant and eicosanoid enzyme inhibition proper-
572 ties of pomegranate (*P granatum*) fermented juice and seed
573 oil flavonoids were studied, which showed strong antiox-
574 idant activity (determined by measuring the coupled
575 oxidation of carotene and linoleic acid) close to that of
576 butylated hydroxyanisole and green tea, and significantly
577 greater than that of red wine.³²

578 This is clearly a fruit worthy of further exploration,
579 especially as most of the information to date relates to the use
580 of the bark, seeds, and the roots as a tenicide (expelling
581 worms). The rind is used as an astringent.^{24,25} The leaf has
582 antibacterial properties and is applied externally to sores.³⁴

583 Date palm (*Phoenix dactylifera*)

584 Body hormones play a central role in skin appearance and
585 are implicated in skin aging. Studies have shown that the
586 decrease of these hormones plays an important role in skin
587 endogenous aging, reduced skin thickness, and the dis-
588 turbance of normal collagen turnover which, in turn, results
589 in a decrease in collagen I and III synthesis. Date palm has 7
590

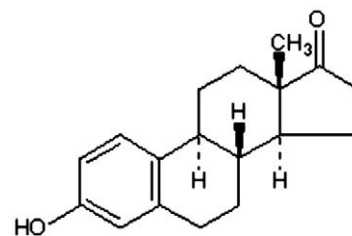


Fig. 30 Estrone.

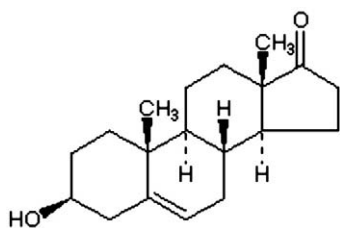


Fig. 31 Prasterone or DHEA.

590 compounds with regenerative, anti-oxidizing, firming, and
 591 soothing properties, extracted from the kernel: phytosterols,
 592 phytosteroids, ursolic acid, isoflavones, policosonols, pro-
 593 vitamin A, and vitamin E.

594 Some studies suggest that dehydroepiandrosterone
 595 (DHEA; Fig. 24) administration would have a beneficial
 596 effect against signs of aging. Dehydroepiandrosterone is
 597 known for its capacity to promote keratinization of the
 598 epidermis or to reinforce the barrier function of the skin.

599 The author compared on ex vivo skin the effects of date
 600 palm kernel extract with those of DHEA in reference to
 601 DHEA as an anti-aging molecule. There was a decrease of
 602 wrinkles within only 5 weeks of date palm kernel extract
 603 application and also improved the skin structure in a way
 604 superior to that of DHEA.¹⁰

605 The seed and the pollen have both been shown to contain
 606 estrone and this may further explain the reasons for this
 607 activity.^{11,28}

608 Hops (*Humulus lupulus*)

609 The hop contains β -sitosterol, estradiol, stigmasterol, and
 610 estrone. In addition, it contains many other materials that are
 611 known for their sedative and relaxing attributes.

612 Regular doses of the herb can help regulate the menstrual
 613 cycle.²¹ It was the girls and women picking hops who first
 614 discovered that hops have an effect on genital organs. Before
 615 machines were introduced, hop pickers used to spend several
 616 weeks at this work, and it had always been known that
 617 menstrual periods would come early in young girls while
 618 they were doing this work. The reason is that hops contain
 619 plant hormones, particularly when very fresh, and these are
 620 similar to estrogens. Considerable amounts have been found,
 621 30000 to 300000 IU of estrogen in 100 g of hops. This also
 622 explains why hops will suppress sexual excitement in men. It
 623 has been shown that there are substances called anti-
 624 androgens that are able to cancel the effects of the male
 625 hormone (androgen).³⁶

626 It was found that hop extract not only recovered the
 627 proliferation of hair follicle-derived keratinocyte suppressed
 628 by androgen but also stimulated the proliferation of hair
 629 follicle-derived keratinocyte. Furthermore, the effects of
 630 hop were evaluated using both animal tests and human
 631 volunteers in vivo. It was demonstrated that hop showed a
 632 potent acceleration on hair growth.²⁹

Sarsaparilla (*Smilax ornate*)

633

634 It is used in concoctions with other plants as a tonic or
 635 aphrodisiac.³³

636 Sarsaparilla was formerly used in the treatment of
 637 syphilis,⁸ gonorrhoea,¹⁸ rheumatism, and certain skin dis-
 638 eases. Used in soft drinks, the genins are also used in the
 639 partial synthesis of cortisone and other steroids.¹⁴ As part of
 640 a wider treatment for chronic rheumatism, it should be
 641 considered as it is especially useful for rheumatoid arthritis.
 642 It has been shown that sarsaparilla contains chemicals with
 643 properties that aid testosterone activity in the body.¹⁷

644 Sarsaparilla contains saponins, sarsapogenin, and parallin,
 645 which yield isomeric sapogenins, sarsapogenin, and smilo-
 646 genin. It also contains sitosterol and stigmasterol in the free
 647 form and as glucosides. It is antirheumatic, antiseptic,
 648 antipruritic, and is indicated for psoriasis, and other
 649 cutaneous conditions. Like other steroidal plants it is
 650 indicated for chronic rheumatism and rheumatoid arthritis.
 651 It is specifically used in cases of psoriasis especially where
 652 there is desquamation.⁴

Sugars, polysaccharides, mucopolysaccharides

653



654 The skin seems to have an affinity for sugars and there are
 655 many examples where they have been shown to have a
 656 significant effect on the skin. Honey is the first choice when
 657 looking for a natural source of these sugars. In third world
 658 countries and poorer communities, honey has been shown to
 659 be of great benefit in the treatment of burns, scalds, and
 660 wounds, especially as it has the additional benefit of having
 661 antibacterial properties when used neat. Re-epithelialization
 662 is improved, the granulation is even, and there is less necrotic
 663 tissue formed. The exudates often associated with severe skin
 664 trauma of this type can be a problem with adhesion to
 665 dressings and to the routine cleaning of the affected site.
 666 Honey absorbs these exudates and makes simple noninvasive
 667 cleaning simple and painless.

668 Mucopolysaccharides are present in numerous plant
 669 materials, such as the ribwort and greater plantains (*Plantago*
 670 and *P officinalis*); these mucilages as they are also called
 671 may be found in numerous species of seaweeds like
 672 bladderwrack (*Fucus vesiculosus*), sea lettuce (*Ulva lac-*
 673 *tuca*), and Oarweed, Tangleweed, or Kombu (*Laminaria*
 674 *digitata*). The use of these plants has similar effects reported
 675 and in the most part they are used for dry, desquamatus,
 676 pruritic skin conditions.

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