CHAPTER EIGHT

What is a phenolic compound, a simple phenol, and a polyphenol?

“First, there’s a molecule called phenol (formerly called carbolic acid), which consists of an aromatic 6-carbon ring with one hydroxyl (-OH) group attached; it’s a simple phenol.

As a functional group (when it is part of or attached to another molecule), this molecular unit is called a phenolic group. If the aromatic ring has more than one hydroxyl group attached it is called a polyphenol (short for poly-hydroxy-phenol).

**Phenolic is an adjective referring to all of these categories.** Among herbal constituents, almost all phenolic compounds are polyphenols.” - Lisa Ganora

In the diagram you can see the benzene structure. In the phenyl group there is an ‘R’ which stands for a group the ring is attached to (instead of just the H) - it becomes a group called a phenyl group. The phenyl group becomes a phenolic when there is at least one hydroxyl group (-OH).

Remember that aromatic refers to the delocalization of electrons - a ‘cloud’ of electrons that are shared equally among the various atoms. The aromatic ring is found in phenolic compounds, some alkaloids and some terpenes. The alternating carbon-to-carbon double bonds in this 6-carbon ring means that the atoms are sharing the electrons.

Do you see the benzene ring structure attached to the sugar molecule (the ‘R’ group)? The ring structure only has one -OH (hydroxyl group) so it is a simple phenol. Specifically it is the simple phenol arbutin.
The major subcategories of the polyphenols include:

Simple Phenol
Phenolic acids
Phenylpropanoids
Coumarins
Furanocoumarins (furocoumarins)
Lignans
Phenylpropanoid derivatives
Stilbenoids
Xanthones
Styrylpyrones

Flavonoids (many subclasses)
Hydrolyzable tannins
Proanthocyanidins & condensed tannins
Isoflavones (isoflavonoids)
Benzofurans
Chromones
Quinones
Phloroglucinol derivatives
Phenolic resins

Simple Phenols
A simple phenol is an aromatic 6-carbon ring with one hydroxyl (-OH) group. It was formerly called carbolic acid.

**Arbutin** is a simple phenol, a phenolic glycoside, is the main constituent in Uva Ursi (*Arctostaphylos uva ursi*), also known as bearberry. Pipsissewa (*Chimaphila umbellata*), Manzanita (*Arctostaphylos manzanita*), etc. also contain arbutin. When arbutin in metabolized, the glycoside releases some **hydroquinone** which concentrates in the urine and contributes to the urinary antiseptic activity. The sugar group (glycoside) adds to the water-solubility.

Hydroquinone, as an isolated ingredient and used in high amounts, is toxic. The amount released from herbal use for urinary tract infections and bladder inflammation is not toxic. Bearberry has been used medicinally since the 2nd century. It should not be used on a daily basis for prevention - it is for short-term, specific use.

**Urushiol** (u -ROO-she-ol) is the oil-soluble, itch-inducing allergen in poison ivy. It is an odd hybrid molecule called a catechol (an aromatic ring with two adjacent hydroxy groups) combined with a saturated or unsaturated fatty-acid like tail. Both diagrams on the left represent the structure of urushiol.

The oil spreads easily on skin - requires soap/saponins to remove.

There is an herb called Jewelweed (*Impatiens capensis*) that when crushed and rubbed **immediately** on poison ivy-exposed skin, can bind the urushiols so that they don’t cause an allergic reaction. However, Jewelweed doesn’t help much once the reaction starts. The saponins in this herb are largely responsible for its ability to wash urushiols off of the skin.
Phenolic Acids

A phenolic acid is a molecule containing at least one phenolic ring along with an acidic carboxyl group (in other words, they are phenolic carboxylic acids). The synonym for phenolic acid is hydroxybenzoic acid (recall the benzene ring structure). All green plants contain phenolic acids, although some accumulate more of these compounds than others do. Most are potent antioxidants and anti-inflammatory agents, e.g., caffeic acid, chlorogenic acid, gallic acid, and ellagic acid.

1. One of the most widely-known phenolic acids is salicylic acid, derived from the naturally-occurring ________________________ glycosides (e.g., salicin, populin) in plants such as Meadowsweet (Filipendula ulmaria), Willow (Salix spp.), Wintergreen (Gaultheria spp.), Sweet Birch (Betula lenta), and various Poplars including Aspen (Populus tremuloides) and Cottonwood.

2. Salicylic acid was originally named ‘spiric acid’ because it was extracted from Meadowsweet which was at that time called Spiraea ulmaria. By adding an acetyl group to spiric acid, early pharmaceutical chemists created the drug aspirin: _______________________________ acid. Only aspirin with its extra acetyl group has significant antiplatelet (blood-thinning) properties.

Other common phenolic acids include ellagic acid, a dimeric compound which occurs in many edible plants including grapes, strawberries, blackberries, raspberries, and pomegranates; it is also a structural component of the ellagitannins. Ellagic acid has been studied for its potent antioxidant and anticancer properties.

3. A recent study found that ellagic acid can induce apoptosis in human ________________ cancer cells. Similar activities have been found with other types of cancer cell lines including colon, prostate, and leukemia (synergistically with quercetin). In addition, ellagic acid has been found to inhibit the development of atherosclerosis by suppressing the aortic smooth muscle cell proliferation induced by oxidized LDL.

4. Gallic acid is found in grapes and wine, walnuts and other nuts, and numerous berries; it also frequently occurs as a gallate unit on many other types of polyphenols including catechins, OPCs, and tannins. Gallic acid has anti-inflammatory, antioxidant, and anticarcinogenic properties; can modulate hepatic detoxification enzymes; and is well-absorbed and readily bioavailable. Historically, it was used by the Eclectics as a systemic ________________ for conditions of the gastrointestinal and urinary systems and as a topical application for ‘purulent conjunctivitis’.

Phenylpropanoids

The phenylpropanoids take their name from the fact that they contain a phenolic ring with a 3-carbon (like propane) attachment. They also have a carboxyl group. These compounds are sometimes called cinnamic acid derivatives, cinnamates, or hydroxycinnamates because their biosynthetic parent compound is cinnamic acid. Phenylpropanoids include chlorogenic acid and its derivative, caffeic acid, commonly found in herbs, fruits, and grains as well as in coffee and cocoa.
5. **Caffeic acid** and its derivatives from the TCM herb _________________ (Salvia miltiorrhiza) have demonstrated antioxidant, anticancer, antimicrobial, and cardioprotective properties. Caffeic acid is also found in Echinacea, where it is a **likely synergist in the antimicrobial, antioxidant, and immunomodulatory properties of the herb**.

6. A derivative, **caffeic acid phenethyl ester** or CAPE (a major constituent of Propolis), has been found to inhibit NF-κB activation, thereby contributing to the anticarcinogenic, anti-inflammatory, and ________________ activities of that potent healing substance.

7. **Chlorogenic acid** has recently been identified as one of the compounds in coffee that is responsible for its ________________ effect. Numerous animal studies have found that this phenylpropanoid slows intestinal absorption of glucose and lowers postprandial glucose levels in insulin-resistant rats), decreases the liver’s output of glucose, and strengthens the function of beta cells in the pancreas.

**Rosmarinic acid** is a phenylpropanoid dimer named after Rosemary (Rosmarinus officinalis) and is found in **many plants of the Lamiaceae and Boraginaceae families**, including Rosemary, Peppermint, Basil, Sage, Thyme, Oregano, Lemon Balm (Melissa officinalis), Bee Balm (Monarda spp.), Perilla (Perilla frutescens), Borage (Borago officinalis), and Comfrey.

**Lemon Balm**: The major compound responsible for GABA transaminase inhibition activity in lemon balm was then found to be rosmarinic acid. Lemon balm is a mildly sedative, calming, and has been shown to improve mood and mental performance. Both Lemon Balm and Bee Balm are considered neuroprotective.

8. **Rosmarinic acid** is a powerful antioxidant and preservative, with anti-inflammatory, antibacterial, and anti-allergic properties. When used **topically**, it has demonstrated antiviral activity against ______________ simplex. **Hydroethanolic extracts of dried Lemon Balm are an especially rich source**. Rosmarinic acid has also been found to act as an antiviral, anti-inflammatory, and neuroprotective agent in a mouse model of encephalitis, where it significantly reduced the incidence of mortality.

9. ______________ extracts from three herbs rich in rosmarinic acid (Lemon Balm, Peppermint, and Sage) have recently demonstrated strong antiviral activity against HIV infection in an in vitro study using human T-cell lines.

**Sage (Salvia officinalis)** has rosmarinic acid and a related compound, **salvianolic acid**.

**Salvia miltiorrhiza** is also known as red sage, Chinese sage, or Danshen. Salvianolic acids are the most abundant **water-soluble** compounds extracted from Danshen. In China it has been used to treat cardiovascular diseases for hundreds of years. Research has shown that the **salvianolic acids** provide **cardiovascular protection**; act as reactive oxygen species scavengers; reduce leukocyte-endothelial adherence; inhibit inflammation and metalloproteinases expression from aortic smooth muscle cells and indirectly regulate immune function. Traditional Chinese medicine uses Danshen to promote blood flow and to resolve blood stasis. It is often used for patients with **angina pectoris, hyperlipidemia, and acute ischemic stroke**. - J Biomed Sci. 2011; 18(1): 30. PMID: 21569331
**Prunella vulgaris** (Heal-all/Self-heal) is non-aromatic (smells like grass) even though it belongs to the Lamiaceae ⁄ Mint family. Bumblebees and butterflies are attracted to this important herb. The constituents in Heal-all include the *rosmarinic acid* (more than Rosemary), caffeic acid, ursolic acid (triterpenoid), immunomodulating *polysaccharides*, bitter principles, etc.. Prunella is antimicrobial (-including herpes), anti-inflammatory, astringent, and antioxidant. An excellent herb to add to daily tonic herbs.

Self-heal was used historically to heal wounds inflicted by sharp-edged tools. In Germany it was used to treat inflammatory **mouth and throat problems**. Chewing the fresh leaves of *Prunella* is effective for bleeding gums, gingivitis, and ulcers. Topically it is used for inflammatory skin problems, ulcers, bites and stings, bleeding from cuts and to reduce swelling. In Chinese medicine Heal-all is a bitter, cold, pungent that **reduces liver fire and nourishes the blood**. 'Liver fire’ can be linked to inflammatory **eye problems** and glaucoma. It helps resolve lumps and nodules (lymphatic system) caused by stagnation of liver qi and accumulation of phlegm and heat.

10. **Echinacoside and cichoric acid are constituents of Echinacea spp.** Echinacoside, derived from caffeic acid, is often classified as a phenylethanoid rather than a phenylpropanoid because instead of having three carbons in one of its side chains, it only has two (ethane is a 2-carbon compound). **Echinacoside has demonstrated antioxidant, ____________, and neuroprotective properties in animal studies.**

11. **Cichoric acid** (named after ____________, *Cichorium intybus*) is another caffeic acid derivative that also occurs in the roots of *E. purpurea*.

12. **Rosavins** is the collective name for three phenylpropanoid glycosides (*rosavin, rosin, and rosarins*) found in the root of Rhodiola rosea; they are thought to be largely responsible for the ____________ and antioxidant properties of the herb. Most Rhodiola extracts are standardized to contain 3% total rosavins.

**Rhodiola:** Studies on isolated organs, tissues, cells and enzymes have revealed that Rhodiola preparations exhibit **adaptogenic effect including, neuroprotective, cardioprotective, anti-fatigue, anti-depressive, anxiolytic, nootropic, life-span increasing effects and CNS stimulating activity**. Encouraging results exist for the use of Rhodiola in **mild to moderate depression, and generalized anxiety**. Lack of interaction with other drugs and adverse effects in the course of clinical trials make it potentially attractive for use as a safe medication. - *Phytomedicine*, 2010 Jun;17(7): 481-93. doi: 10.1016/j.phymed.2010.02.002.

Rhodiola is classified as a mild stimulant but at high doses or when combined with high caffeine drinks it may cause anxiety or insomnia - the opposite reason it is often used.

Most of the phenylpropanoids are antioxidant, antimutagenic, antitumor, and/or antimicrobial to some degree. **Most are soluble in hot water or hydroethanolic media.** However, a few of the phenylpropanoid derivatives are oil-soluble and occur as **components of certain essential oils:** anethole (a carminative from Anise), apiole (an antispasmodic from Parsley), cinnamaldehyde (an antimicrobial from Cinnamon), and eugenol (an antimicrobial from Clove) are common examples.
13. **Safrole**, found in the tasty essential oil of Sassafras (*Sassafras albidum*) is a phenylpropanoid that has gained a reputation as being ‘carcinogenic’. This is true when the isolated compound is given to laboratory rats in high doses; in this context, safrole is an established low-grade hepatocarcinogen. However, drinking Sassafras tea has not been associated with the development of cancer in humans; it would be difficult to get significant doses of safrole from a water infusion. Traditionally, Sassafras tea is highly regarded as a ‘fall tonic’ and ‘blood cleaner’ in the Appalachians. **All things considered, it’s probably a good idea to avoid concentrated____________________ of Sassafras.**

14. **Eugenol** is found mainly in the essential oils of _________________ (*Syzygium aromaticum*) buds (where it accounts for ~ 75–90% of the total oil) and in Cinnamon bark (~ 1–13%) and leaf (~ 40–90%). This highly active constituent is antiseptic, anesthetic (topical), antioxidant, antimitotic, antispasmodic, anti-inflammatory, and antifungal; inhibits platelet aggregation; suppresses NF-κB activation; and, in large excess, is caustic, convulsant, hepatotoxic, a CNS depressant, and induces hemostatic abnormalities.

**Coumarins**

Coumarin was the common name for the tonka bean (*Dipteryx odorata*), from which the simple compound coumarin was first isolated in 1820. The phenolic compounds called coumarins occur mainly in members of the Fabaceae and Poaceae families (legumes and the grasses) and they are familiar to us through our sense of smell; **coumarins are responsible for that lovely new-mown grass or fresh-cut hay aroma.** Coumarins are not the curcuminoids (curcumin, etc.) found in turmeric.

15. In plants, coumarins generally exist in the form of glycosides such as melilotoside from **Yellow Sweet Clover** (*Melilotus officinalis*). When the plants are injured, coumarin and its relatives are released from their glycosidic precursors. These compounds are actually a type of phenylpropanoid derivative, **a cyclic ester (also called a ____________) fused to an aromatic ring: the characteristic coumarin skeleton.**

The most common coumarins include coumarin itself; melilotoside, esculetin and its glycoside esculin (synonym: aesculin) from the bark and seed husks of the horse chestnut (*Aesculus hippocastanum*) tree; *scopoletin* and *scopolin* which occur in several plants including poppies, nightshade family herbs, and grapefruit; and *umbelliferone* with its glycoside *skimmin*, which are distributed throughout the Apiaceae (carrots, parsley, celery, parsnip, Angelica, Queen Anne’s lace (*Daucus carota*), etc.

**Coumarins in general** are antioxidant, anti-inflammatory, and tonic to the venous and lymphatic vessels; they are featured in plants traditionally used to treat conditions such as edema, varicose veins, and hemorrhoids.
16. **Horse chestnut tree bark** is perhaps the richest known source of **esculin** (up to 8%) and a closely-related glycoside, **fraxin** (up to 3%). These coumarin glycosides have demonstrated antioxidant and photoprotective activity against UV-generated free radicals; fraxin in particular is a potent mediator of hydrogen-peroxide induced oxidative stress, with anti-inflammatory and antimetastatic properties. In Horse chestnut, the coumarins have been found to work synergistically with the _________________ to bring about the herb’s protective and tonic effects for the venous and lymphatic vessels. **Butcher’s Broom (Ruscus aculeatus)** is used for a similar purpose.

To reiterate, the natural coumarins themselves have little anticoagulant activity; but a fungal metabolite, dicoumarol, is a powerful hemorrhagic compound. **Dicoumarol can form in moldy or poorly dried coumarin-rich plant material such as Sweet Clover.**

### Furanocoumarins

Furanocoumarins are phytoalexins based on the **c**oumarin **skeleton with the Addition of a furan ring.** Many of these compounds are **phototoxic and/or photoactivated**, meaning that their physiological properties appear when they are stimulated by UV light. The most common furanocoumarins examples include **bergapten, xanthotoxin, and psoralen.** The essential oil of Bergamot is prepared so as to avoid an excessive concentration of furanocoumarins and the consequent possibility of skin irritation.

Celery, especially if infected with a fungus, can produce a high enough level of furocoumarins to give its handlers a Poison Ivy-like rash; this effect has also been elicited by other Apiaceae family vegetables (e.g., Parsnip, Parsley) and herbs including Angelica spp. and Rue (Ruta spp.). Lime, Grapefruit, and Bergamot are among the citrus fruits that can develop problematic levels of furanocoumarins.

**Giant Hogweed:** One of the worst phytophototoxic reactions has been known to occur in some people when they are exposed to sunlight along with the furocoumarins in Giant Hogweed (**Heracleum mantegazzianum**). Such exposure can cause severe burn-like blisters that leave scars and hyperpigmented areas on the skin for many years. Additionally, if **Heracleum** sap gets into the eyes, it can cause blindness. However, just like with Poison Ivy, there are some people who seem to be relatively insensitive to the effects of Giant Hogweed.

17. In Grapefruit juice, **bergapten** and its derivatives have been found to inhibit a number of cytochrome p-450 enzyme isoforms. The flavonoid co-constituent **naringenin** and its glycoside **naringen** are also known to inhibit a number of other CYP isoforms. If a person is taking pharmaceuticals which are broken down by any of these specific enzymes, they may be advised to avoid drinking grapefruit juice so that excessive levels “of the drugs do not _______________ in the body.

18. On the other hand, the furanocoumarins in **grapefruit juice** have therapeutic potential: they have demonstrated significant antibacterial activity, inhibiting pathogenicity and the formation of ________ by species including *Escherichia coli, Salmonella typhimurium,* and *Pseudomonas aeruginosa.*
**Note:** Naringenin possesses the distinct bitter taste of grapefruit juice. It is a strong antioxidant that some ability to prevent carbohydrate absorption from the intestines, possibly reducing rapid rises in blood sugar and insulin after eating. This could have some beneficial effect on weight management and metabolic syndrome. Naringenin is one of the major citrus flavonoids predominantly found in grapefruit, oranges, and tomato skins.

### Lignans

The lignans are a very diverse group of compounds but they are all formed by joining together units called hydroxycinnamyl alcohols, derived from phenylpropanoid precursors. Various kinds of lignans are known to contribute to the activity of adaptogenic, phytoestrogenic, hepatoprotective, and anticarcinogenic herbs. Lignans are sometimes confused with lignin, the tough, woody polymer that strengthens some plant cell walls and seed coats.

19. Two beneficial, non-oil soluble lignans occurring in Flaxseed are secoisolariciresinol (existing mainly in the form of secoisolariciresinol diglucoside or SDG) and matairesinol. In the body, they are metabolized by the colon microflora into enterodiol and enterolactone, which are called the __________ lignans. Evidence suggests that a healthy colon flora population may be necessary for humans to derive significant benefit from lignans in plants.

A clinical trial with postmenopausal women found that Flaxseed supplementation favorably altered the balance of ‘good’ (2-hydroxylated) vs. ‘bad’ (16-a-hydroxylated) estrogen metabolites in a dose-dependent manner. Another study reported that Flax significantly lowered estradiol and estrone sulfate levels in postmenopausal women while increasing prolactin levels. Current research indicates that high levels of lignans are associated with lower breast cancer risk... The researchers suggested that there could be a threshold phenomenon in which lignans provide the greatest protective effect among women who have higher endogenous hormone levels, and presumably, higher breast cancer risk.

20. Numerous epidemiological studies have shown an inverse correlation between cancer incidence and fruit and vegetable consumption; lignans are among the many compounds likely to be responsible for this effect. It has also been demonstrated that women with breast cancer have lower _______ levels of lignans than women without breast cancer.

21. **Sesamin**, a lignan found in sesame (*Sesamum indicum*) seeds, has antihypertensive, cardioprotective, antioxidant, anti-inflammatory, and hepatoprotective properties and enhances the ability of tocotrienols to protect the skin from UV radiation. Like the lignans from flaxseed, it is metabolized by the colon ________ to become enterolactone, so it would be reasonable to expect that it acts similarly to secoisolariciresinol inside the body.

22. **NDGA** (*nordihydroguaiaretic acid*) is a strongly antioxidant, anti-inflammatory, and anticancer compound found in *Creosote Bush* (*Larrea spp.*) and Guaiac. NDGA is well-known to inhibit lipoxygenase activity and has also been found to inhibit tumor growth in a mouse model of breast cancer. However, several animal studies have found that high doses of this constituent can have hepatotoxic or nephrotoxic effects and there are several case reports of Larrea-associated liver problems. Traditionally, the herb has been used in the form of a tea; this would limit exposure to NDGA, which is a ______ constituent with very low solubility in water.
23. **Schizandra** (*Schizandra chinensis*) berry, also called Wu Wei Zi or 'five flavor berry,' contains a number of lignans called the **gomisins** and **schizandrins** that contribute to its antioxidant, adaptogenic, hepatoprotective, and ____________ effects.

![Milk Thistle](image)

**Milk Thistle** (*Silybum marianum*), a name which refers to the milky-white venation of the leaves, contains the most powerful hepato-protective and hepatoregenerative compounds known. **Flavonolignans** are hybrid molecules sharing characteristics of both flavonoids and lignans. The flavonolignan silymarin (a collective term) is three individual compounds: silybin, silydianin, and silychristin.

24. Silymarin is an extraordinary substance that acts as an antioxidant for lipids and protects cell membrane integrity in the liver. It is **not very water-soluble, but is soluble in ethanol**. In some dietary supplements, the silymarin is complexed with ____________ (in the form of liposomes) in order to enhance its bioavailability.

25. Milk thistle _____ can be ground like flaxseed and added to the daily diet as a nourishing antioxidant liver tonic. Standardized, concentrated extracts of Milk Thistle are available and are often recommended by practitioners for therapeutic use (e.g., with hepatitis) because the substance works well and is **non-toxic in high concentrations**.

**Phenylpropanoid Derivatives**

There are a few other unusual and medicinally important compounds derived from phenylpropanoid precursors. These include the **curcuminoids** (from Turmeric, *Curcuma longa*); the **gingerols** and **shogaols** (from Ginger, *Zingiber officinale*), and the **capsaicinoids** from the spicy members of the Capsicum genus (e.g., Cayenne Peppers).

The most famous of the curcuminoids compounds is **curcumin**, structurally classified as a diarylethenoid – meaning it contains two aryl (aromatic) rings joined by seven carbon atoms. Curcumin has pronounced antioxidant, antimutagenic, antiviral, antifungal, antibacterial, anti-inflammatory, nephroprotective, hepatoprotective, neuroprotective, and choleretic properties; and induces apoptosis in several types of cancer cells. Turmeric is highly regarded in both Ayurvedic and Western herbal traditions as an alternative to NSAIDs or COX-2 inhibitors, as a bitter tonic and remedy for the digestive system, and as a healing, detoxifying herb for the liver.

26. Curcuminoids are ____________ compounds and medicinal quantities are obtainable from freshly powdered turmeric (for example, in curry sauces); **Coconut oil or other dietary oils enhance their absorption**. Supercritical CO2 extracts are an excellent source for therapeutic use and provide an even more concentrated dose of these compounds.

27. The **gingerols** and **shogaols** share curcumin’s anti-inflammatory properties. Gingerols are the pungent, resinous compounds (not water-soluble) found in fresh Ginger rhizomes. Some of the gingerols change into shogaols when the rhizome is dried. **They extract quite well into hydroethanolic media, __________, and supercritical carbon dioxide.**
In addition to helping relieve inflammation, **gingerols** and **shogaols** are **antiemetic** (alleviate nausea), **antioxidant**, stimulate the circulation, and along with a closely-related compound, 8-paradol, help to modulate platelet aggregation for an **aspirin-like blood-thinning** effect. They have also demonstrated **anticancer** properties.

A recent study found that **6-shogaol** in particular inhibited the growth of human colorectal cancer cells and induced apoptosis via modulation of mitochondrial functions involving reactive oxygen species. **Gingerols** and the corresponding shogaols are cytotoxic towards a range of cancer cell lines. Tumors induced in several animal models were successfully treated by gingerols.

![Gingerols and Shogaols](image)

Found only in the *Capsicum* genus plants, the **capsaicinoids** include the familiar and dramatically spicy compound capsaicin along with dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin.

28. The capsaicinoids are ________, oil-soluble phenylpropanoid derivatives, structurally classified as vanillylamides (derived from vanillin, and containing an amide functional group). While the aromatic ring of these molecules originates from phenylalanine via vanillin, the aliphatic tail comes from a branched-chain fatty acid; and the amide function is derived from an amino acid. Because of this latter feature, some authors classify the capsaicinoids as alkaloids or pseudoalkaloids. **Capsaicin** is a potent topical anodyne (upon repeated application, it depletes substance P, a neurotransmitter which communicates pain signals).

29. As we know from both the scientific literature and practical experience, it is also an antiseptic gastric stimulant and a vasodilator with pronounced _________ and rubefacient activity. In addition, this mighty little molecule (capsaicin) suppresses NF-κB activation, which may contribute to the anti-inflammatory, anticarcinogenic, and immunomodulating properties of Cayenne.

**Stilbenoids**

There are relatively few stilbenoids in the plants we use therapeutically, with the exception being **resveratrol**. Stilbenoids contain the stilbene core, which consists of two aromatic rings joined by two carbons that are double-bonded to one another. This structural unit is part of many molecules (both natural and synthetic) that have **estrogenic or antiestrogenic activity**. Resveratrol is a very mild, protective estrogenic modulator.

Although **resveratrol has anticarcinogenic effects**, the synthetic stilbenoid known as DES (diethylstilbestrol) is a powerful multi-generational carcinogen. DES was first prescribed to prevent miscarriage in the 1940s; it was later found to increase the risk of certain rare cancers and other abnormalities in the reproductive systems of both the mother and infant. Even some of the DES granddaughters are showing effects of this ‘warped’ stilbenoid. **Tamoxifen**, the selective estrogen receptor modulator (SERM) drug that is currently popular as a treatment for breast cancer, also has a stilbene core.
30. Resveratrol is an antifungal phytoalexin made by a few plants including Japanese Knotweed (*Polygonum cuspidatum*) and Grape (seeds and skins), and is found in lesser amounts in many blue/red/purple berries. It has numerous ___________, antioxidant, and cardioprotective benefits for humans. In addition, it is an anti-inflammatory COX-1 modulator with venotonic effects, inhibits platelet aggregation, induces apoptosis in certain cancer cells, and acts as a beneficial phytoestrogen that may help to prevent or treat breast cancer.

31. Resveratrol is **ethanol-soluble**, so significant amounts are found in red wine (tincture of Grape skins). Many resveratrol supplements are made from the __________ of Japanese knotweed, which is the richest known practical source of the compound – and being an invasive weed, it’s also an ecologically sustainable choice!

![Pinosylvin](image)

**Pinosylvin** (3,5-dihydroxy-*trans*-stilbene), is a naturally occurring resveratrol analog found in heartwood (non-living center of the tree trunk) and leaves (needles) of *Pinus* species. The Pinaceae (pine family) are trees or shrubs, including many of the well-known conifers such as cedars, firs, hemlocks, larches, pines and spruces. Pinosylvin is a is a **pre-infectious phytoalexin** that protects the tree from fungal infections. Many phytoalexins are produced in plants in response to an infection.

In the human body, pinosylvin has **antioxidant, antifungal, algicidal and nematocidal** activities. The antibacterial and antifungal activities of pinosylvin, were studied and compared with those of resveratrol. Pinosylvin exhibited more potent growth inhibitory activity against *Candida albicans* and *Saccharomyces cerevisiae*.

### Xanthones

Xanthones (the root xanth means yellow) are brightly-pigmented antioxidants that occur in only a few medicinal plants. The basic xanathone structure contains two phenolic rings fused to a central pyranone ring (hence the –one suffix).

32. St. John’s Wort contains a variety of xanthones including __________, which you can see in its bright, sunny yellow flowers. These compounds act **synergistically** with the other co-active molecules (hypericin, hyperforin, the flavonoids, etc.) to bring about Hypericum’s antidepressant activity.

![St. John's Wort](image)

**Repeat from synergy:** St. John’s Wort (*Hypericum perforatum*) is known to contain **at least five different constituents which contribute to its activity as an antidepressant**. The first to be identified were **hypericin** and **pseudohypericin**, both belonging to the class of polyphenols called bianthraquinones (synonym: naphthodianthrones). Subsequent research found that a phloroglucinol derivative, **hyperforin**, worked synergistically with the hypericin. Later studies identified the xanthone **norathyriol** and the flavonoid **hyperin** as important synergists. Small amounts of melatonin, an aromatic amine, are also found in the plant. **Various combinations of these compounds, as well as broad-spectrum extracts of the herb, have been found to have greater activity than any individual constituent alone.** Exactly how these compounds work together is still being studied.
33. The **mangostins are a group of closely-related xanthones** that give Mangosteen (Garcinia mangostana) fruit a yellowish tinge; several animal studies have identified antimicrobial, antioxidant, anti-inflammatory, and cardioprotective effects. The mangostins, **norathyriol**, and its glycoside, **mangiferin**, have also been found to have anticarcinogenic activities. Norathyriol, in particular, has potent anti-inflammatory properties. The latter two compounds are also found in the fruit of the ___________ (Mangifera spp.).

34. Another potentially active xanthone is ___________, one of the pigments found in Yellow Gentian (Gentiana lutea) and in *some species of Hypericum*. Although research is lacking, it has been speculated that gentisëin may have activities similar to those of the other xanthones.

**Newer research:** The xanthones, including gentisëin, in Gentian has shown hepatoprotective, anti-inflammatory, and anticancer activities. The root of several Gentian species is used as a bitter tonic which stimulates the flow of gastric juices, increases appetite and aids in digestion. It also strengthens a weak or under-active digestive system.

**Styrylpyrones**

The styrylpyrones are a small group of phenolic compounds, biosynthetically descended from cinnamic acid (the parent compound of the phenylpropanoids). So far, they have only been found in plants of the **Lauraceae and Piperaceae families**. In the latter group we have the important medicinal and social/ritual herb, Kava (*Piper methysticum*).

The specific styrylpyrones in Kava (*Piper methysticum*) are called either **kavalactones** or **kavapyrones**; you can see how both names apply by looking at the structure: the lactone ring (which is also a pyrone ring) is the common feature.

35. The **kavalactones include kavain** (antispasmodic, anti-inflammatory, anti-edemic), **methysticin**, and **yangonin** (both antispasmodic). These compounds have low solubility in water, and are usually extracted with ___________ ethanol or with organic solvents like acetone. Traditionally, they are dissolved in fat-rich coconut milk.

36. The three kavalactones work together synergistically, and help to produce the gently sedative, emotionally and physically relaxing, and spiritually uplifting effect of Kava. They are also synergistic modulators of a number of cytochrome p-450 enzymes and p-glycoprotein. A recent Cochrane review has found Kava to be decidedly beneficial for treating anxiety and the kavalactones have demonstrated ___________ activity which may help to protect the brain against Alzheimer's disease and oxidative stress.

*Kava*-containing products were banned in Western countries such as Germany, France, Switzerland, Australia, and Canada, following reports of alleged hepatotoxicity. We have previously demonstrated that kava alkaloid, **pipermethystine** (PM), abundant in *leaves and stem peeling*, induces **mitochondrial toxicity in human hepatoma cells**, HepG2, as compared with the bioactive components, kavalactones, abundant in the rhizome. *Toxicol Sci.* 2007 May;97(1):214-21. Epub 2007 Feb 27.
Although kava drink is traditionally prepared from the underground roots and rhizome, commercial preparations in the late 1990s may have included stem peelings and above-ground parts due to easy availability and high demand. Stem peelings and leaves contain high concentrations of kava alkaloid, pipermethystine, as compared to the physiologically active kavalactones that are abundant in roots and rhizome. Traditionally, kava has been safely consumed for centuries without much documented adverse hepatotoxicity. https://doi.org/10.1093/toxsci/kfm035

Flavonoids

The word root flav means yellow; some flavonoids (those first to be discovered, thus giving their name to the entire class) are yellow; but others are red, blue, purple, or even colorless. Even dark leafy greens are flavonoid-rich but the chlorophyll hides the color. The basic structure of a flavonoid consists of two phenolic rings, with varying numbers and kinds of substituents, joined in the middle by a central pyran ring.

Every green plant biosynthesizes a range of flavonoids, which serve as antioxidants to protect the plant’s tissues against free radical damage. These compounds often occur in the form of water-soluble glycosides, intermixed with the more lipophilic aglycones. There are numerous subtypes, some widely distributed and others limited to a smaller number of species.

As we discuss the subtypes below, notice that the specific spelling tells us which functional groups and/or double bonds appear in the central ‘C ring’ of the molecule.

The FLAVA– prefix means there is NO double bond in the C ring itself.

The FLAVO– prefix indicates there is a double bond between C2 and C3.

You’ll also notice various –ONES (ketone) and –OLS (alcohol/hydroxyl groups) in the names of the flavonoid subtypes.

Note: The flavonoids are the largest subclass of polyphenols, more than 4,000 types. These compounds are becoming established as major contributors to the cancer-preventative, anti-aging, and health-promoting effects of berries, fruits, vegetables, leafy greens, dark chocolate, and coffee. In general, the flavonoids are anti-inflammatory, anticarcinogenic, antioxidant, and cardioprotective.

“Flavonoids actually communicate with our genes, and are part of the environmental epigenetic factors that influence gene expression. In other words, they can encourage different genes to switch on or off, which regulates cellular behavior and products. Some of this activity results in protective effects and anticancer activity.” -Lisa Ganora

In the large intestine, gut microbial enzymes transform flavonoids into metabolites that can then be absorbed or excreted. The diversity and activity of colonic bacteria, will determine which metabolites can be produced from ingested flavonoids. The composition of the colonic microbiota can therefore affect the metabolic fate and bioavailability of dietary flavonoids. https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/flavonoids
Phenolic Compounds/Polyphenols (Major Category) - Flavonoids (Subcategory)
Subtypes/Subclasses of Flavonoids:

Chalcones - biosynthetic precursors of all flavonoids
  Hops: xanthohumol, 8-prenylnaringenin; antiandrogenic
  Licorice: lichochalones, isoliquiritigenin, butein; anticarcinogenic

Flavanols - strong antioxidants, mild astringents, anticarcinogenic
  catechin, epicatechin, epigallocatechin (EGC), epigallocatechin gallate (EGCG),
  epigallocatechin digallate (EGCDG), etc.

Proanthocyanidins (condensed tannins) - antioxidant, cardioprotective, anti-inflammatory

OPCs (oligomeric proanthocyanidins)
  Grape seed & skins extract, pine bark extract
  Hawthorn is rich in OPCs (esp. flowers, leaves)

Hydrolyzable tannins - antibacterial, antioxidant, anti-inflammatory, astringent
  gallotannins, ellagitannins
  found in many astringent herbs, including white oak, witch hazel, strawberry leaf, etc.

Anthocyanidins (aglycones)/Anthocyanins (glycosides) - antioxidant, anti-inflammatory
  cyanidin, delphinidin, pelargonidin, malvidin, peonidin, petunidin
  pink-red-purple-blue pigments in flowers, fruits, berries, red onions, purple cabbage, etc.

Flavonols - antioxidant, anti-inflammatory, anti-allergic
  quercetin, rutin (a glycoside of quercetin), hyperin (a glycoside of quercetin)
  kaempferol, myricetin, isorhamnetin
  many vegetables, fruits & berries, many spices & herbs, leafy greens; widely distributed

Flavones - generally anti-inflammatory, antispasmodic, anticarcinogenic, & antibacterial
  luteolin, apigenin, & several glycosidic forms
  rich sources: parsley, dandelion flowers, thyme, peppermint, rosemary, oregano

Flavanones - also called bioflavonoids or vitamin P - all are antioxidants
  naringenin (glycoside: naringin): CYP-450 inhibitor in Grapefruit
  hesperetin (glycosides: hesperidin, neohesperidin)
  eriodictyol (Yerba Santa - Eriodictyon): glycosides: eriocitrin, eriodyctin, neoeriocitrin
  liquiritigenin (Licorice; glycoside: liquiritin)
  rich source of flavanones: Citrus spp.

Isoflavones (isoflavonoids) - isoflavones are phytoestrogens
  biochanin A, formononetin (from Red Clover, Kudzu)
  genistein, daidzein, glycine (from Soybeans)
**Anthocyanidins (glycosides: anthocyanins):** These compounds are the blue/red/purple pigments that we see in many flowers and fruits (e.g., aronia berries, bilberry, blueberry, blackberry, elderberry, currants, blood orange) and red/purple vegetables (e.g., cabbage, eggplant, colorful potatoes). They are characterized by having a positive charge on the oxygen atom of the central C ring, which associates with a negative ion such as chloride. Because this structure has a positive charge, it is technically called a flavilyum ion. Anthocyanins exhibit a wide range of antioxidant protection and health benefits including cardioprotective, neuroprotective, anti-inflammatory, and anticarcinogenic properties.

**Bilberry** are the source of pharmaceutical grade anthocyanins, in U.S.P. Bilberry contains over fifteen different aglycones and glycosides of cyanidin, delphinidin, malvidin, peonidin, and petunidin. It also facilitates the regeneration of rhodopsin which improves night vision. Bilberry is anti-inflammatory, antioxidant, anticancer, and improves vascular and lymphatic vessel integrity.

37. The most widely distributed representatives of anthocyanidins include **pelargonidin, delphinidin, and________________**, with their numerous glycosides. Anthocyanins are also present to some degree in all green leaves, where they are the companions of chlorophyll.

"Fruits with a preponderance of **pelargonidin glycosides** have an orange–red color, as opposed to a deep red color with cyanidin glycosides. Aglycones generated from the most abundant anthocyanins, such as delphinidin, malvidin, and **pelargonidin** exerted a marked inhibitory effect on all cell lines tested (cancer cell lines for colon, stomach, lung, and breast); while cyanidin, petunidin and delphinidin showed such inhibitory effects only in breast cancer cells." - Ortensia Ilaria Parisi, Francesco Puoci, in Polyphenols in Human Health and Disease, 2014

**Colors:** The colors blue/red/purple are not exclusive to anthocyanidins. The betalain alkaloids (named after beets), rainbow chard, spinach, pokeweed, prickly pear, etc. give them the same beautiful colors. **The plants that contain phenolic anthocyanin pigments do not contain betalains and vice versa.**

38. **Aurones** are yellow and golden yellow pigments found in some fruits and flowers, but for the most part their medicinal actions have yet to be discovered. Some aurones are antifeedants, discouraging insect predation; others glow in the ultraviolet spectrum and form patterns on flowers that attract________________.

39. **Chalcones** (yellow/copper color) are the parent compounds, the precursor of all other subclasses of flavonoids. They have an ‘open ring’ as their central structure. A few chalcones have known medicinal activities. In **Licorice**, several chalcones with________________, antioxidant, and anticarcinogenic properties have been identified (e.g., butein, isoliquiritigenin, licochalcone A).

A glycoside of isoliquiritigenin inhibits aldose reductase (anti-cataract activity). Licochalcones are antiparasitic (Leishmania, Malaria, ect.). Butein has been shown to stop the growth of melanoma cell in vitro (lab). Chalcones and aurones are found in many flowers.
40. **Hops** (*Humulus lupulus*) contains a number of prenylated chalcones that have ____________ physiological activities, including **xanthohumol** which is antioxidant and anticarcinogenic. A close relative of xanthohumol, desmethyloxanthohumol, and its derivative 8-prenylnaringenin, are potent phytoestrogens; and 6-DMA-N, another prenylated chalcone derivative found in **Hops**, is strongly anti-androgenic.

**Hops**, if fresh, should have a bright golden color. If they are lacking color they are good for compost! Hops are antioxidant, calming, relaxant, anti-inflammatory, and antimicrobial. **Xanthohumol** is a major flavonoid in hops. It is a very bitter, resinous, oil-soluble constituent found in the **strobes** (female cones). The other bitter, antioxidant, and antibacterial molecules found in hops strobiles are **phloroglucinol derivatives**: **humulone** and **lupulone**. (-one/ketone). While 8-prenylnaringenin is a potent phytoestrogen, hops contain very small amounts.

**Flavanols**: Most that have been studied for medicinal activity are also known as flavan-3-ols, indicating that they have a hydroxyl group attached to C3 of the saturated central ring. The most famous flavan-3-ols are those from **Green Tea**: **catechin** and **epicatechin**.

41. Green Tea also contains larger derivatives of the catechins, formed by adding various numbers of hydroxyl groups or gallate units to the epicatechin nucleus. These compounds, soluble in hot water, include **epigallocatechin** (EGC), **epigallocatechin gallate** (EGCG), and **epigallocatechin digallate** (EGCDG). The flavan-3-ols in Green Tea – especially ______________ – have antioxidant, antiangiogenic, and pro-apoptotic properties for an anticancer effect; are anti-atherosclerotic, antihypertensive, and cardioprotective.

42. When tea is steeping, the larger catechin derivatives are slower to extract into the water than are the smaller, less ______________ ones. You can taste this phenomenon by comparing the flavor of Green or Black Tea steeped for one minute to an infusion that has been sitting for an hour or more.

**Note**: It is easy to see why catechin and epicatechin molecules are easily extracted in hot water - many hydroxyl goups (-OH).

43. **Flavanones**: (flav AN ON es) are prominent in citrus fruits where they concentrate in the albedo. Flavanones, named after the fact that they have a ketone functional group on the central ring but lack a double bond between C2 and C3, are often referred to as ______________. Collectively, they have also been called **vitamin P**, for permeability factor.

44. Flavanones help to regulate capillary permeability and tonify the blood vessels. The disease known as scurvy is often blamed on a vitamin C deficiency, but as long ago as 1938 the discoverer of vitamin C noted that the symptoms of excessive bleeding and bruising are largely due to a concomitant lack of 'vitamin P,' which always occurs along with vitamin C in Nature. **Hesperetin** and its glycoside, ______________, are common flavanones from citrus fruits (which botanically are called hesperidia).
45. __________________, a flavanone glycoside, is a cytochrome p-450 inhibitor found in high concentrations in grapefruit (along with the furanocoumarin bergapten) These compounds can decrease the liver’s metabolism of certain drugs, thereby increasing their levels in the blood.

46. Other antioxidant flavanones (e.g., eriodictyol, liquiritigenin) are found in herbs such as Rosemary, Yerba Santa (Eriodictyon californicum), and Licorice. Liquiritigenin (glycoside: liquiritin) contributes to the anti-inflammatory, anti-allergic, and antispasmodic action of the flavonoid fraction of licorice. Along with numerous other flavonoids in the herb, it may have ______________ activity and is antibacterial. In addition, it was recently discovered that liquiritigenin….can be expected to have beneficial phytoestrogenic effects on menopausal symptoms (e.g., hot flashes and bone loss)...

**Flavones** (flav ON es): their name tells us that the central ring has a ketone function but lacks the hydroxyl group of the flavonols. There is also a **double bond** between C2 and C3. In general, the flavones are anti-inflammatory, anticarcinogenic, antioxidant, antispasmodic, and antimicrobial.

47. Among the richest sources are the Mediterranean culinary herbs including parsley, rosemary, thyme, and oregano. Flavones are also featured in red peppers (both sweet and hot), artichoke, celery, and chamomile. **Luteolin** is perhaps the most studied compound in this group; rich sources include peppers, dandelion ______________ and leaves, lemon balm, peppermint, perilla leaves, and the Mediterranean herbs.

48. **Luteolin** – not to be confused with the similarly-named carotenoid lutein – has pronounced **anticarcinogenic** (cell-growth-regulating and apoptosis-inducing) properties in numerous different types of cancer cells including oral, prostate, lung, and colon cancers. In the flowers of the Dandelion, luteolin and its glycosides act ______________ with other flavonoids and the carotenoid constituents for an antioxidant and cancer-prevention effect.

49. **Apigenin** (glycoside: apin), a flavone notably concentrated in ______________ and other Apiaceae family plants, has anti-inflammatory and antispasmodic properties. Both flavones appear to have **numerous physiological activities** and have been the subject of considerable research. A recent study found apigenin and luteolin to have a protective effect on the insulin-secreting cells (beta cells) in the pancreas.

50. **Baicalein**, its glucuronate conjugate baicalin, and **wagonin** are flavones found in the **root of Baical Skullcap** (Scutellaria baicalensis), an herb long used in TCM for treating allergies, inflammation, and cancer. These compounds have antimutagenic, anti-inflammatory, and antioxidant properties. Researchers found that the extract reduced ______________ tumor volume in mice by 50% after only 7 weeks of treatment. A recent Polish review reports that these flavones have beneficial effects for the cardiovascular system, including regulation of platelet aggregation and capillary permeability. In addition, they have demonstrated significant protective action on the cardiomyocytes.
**Flavonols** (flav ON OL s): These yellow flavonoid pigments are often hidden by the stronger colors of other compounds. Their name indicates that they have both ketone (–one) and hydroxyl (–ol) groups on the unsaturated central ring. **Isorhamnetin** and **kaempferol** are common flavonols that act as co-pigments to the anthocyanins in green plants, where they help to quench UV-generated free radicals.

51. **Quercetin**, a potent sulfur-colored flavonol, **inhibits mast cell degranulation for an anti-allergic and anti-inflammatory effect**; it is also a powerful anticarcinogenic and carcinostatic compound. Rich dietary sources of quercetin include Onion – and not just the skin, as some have written; Kale, Broccoli, ____________ (Vaccinium vitis-idaea), Cranberry, Black Currant, Green Tea, and Fennel. It is found in numerous other plants as well.

52. There are many different glycosides of quercetin in medicinal plants, including **hyperin** (quercetin-3-galactoside or hyperoside), a major flavonoid in **Hawthorn** (Crataegus spp.) where it acts as a ______________ antioxidant and anti-inflammatory agent. A recent study has found that metabolites of quercetin accumulate in human arterial tissue when atherosclerosis threatens, acting as localized vascular antioxidants.

**Hyperin** also protects against cataract development via inhibition of lens aldose reductase; has in vitro antiviral activity against hepatitis B; and occurs in **St. John’s Wort** as a synergistic contributor to the antidepressant activity, where it enhances the bioavailability of other constituents.

**Note:** There are more than 135 different glycosides of quercetin occurring in various leaves, flowers, and fruits.

53. **Rutin** (quercetin-3-rutinoside), featured in Citrus, Rheum, Polygonum, and Fagopyrum species, Horse Chestnut, Butcher’s Broom, and ____________ (Ruta graveolens) after which it is named, strengthens the capillaries and is venotonic for a beneficial effect on varicose veins, ‘spider’ veins, leg edema during pregnancy, and hemorrhoids. It is also found as a **synergist in St. John’s Wort**. Some of the major antioxidant, anti-inflammatory, and neuroprotective compounds in **Ginkgo** are also flavonol glycosides (based on the aglycones quercetin, kaempferol, myricetin, and isorhamnetin).

54. **Kaempferol** was recently identified as an inhibitor of the aryl hydrocarbon receptor, which is activated by many potentially carcinogenic compounds (e.g., polyaromatic hydrocarbons and polyhalogenated hydrocarbons) in cigarette smoke, ______________, etc...Along with its antioxidant and anti-inflammatory properties, this would suggest that kaempferol can help to protect against lung cancer. Kaempferol is widely distributed; rich sources include Broccoli, Kale, and dark leafy greens.

55. Almost all of the flavonoids have some hormonal activity. However, the flavonoids do not always bind to alpha or beta estrogen receptors), as do the **isoflavones**; Because of this, they **exert an influence on estrogen-sensitive cells and tissues in the body** – where they have more of an anti-estrogenic effect as opposed to a pro-estrogenic one. In other words, these compounds enhance the normal regulation of cell growth and thereby inhibit the runaway reproduction of cancer cells. Two of the most active cell-growth regulators are quercetin (a flavonol) and ______________ (a flavone).
Hydrolyzable Tannins are astringent antimicrobial compounds constructed of several hydroxyl-rich phenolic segments joined to a central molecule of sugar. They are called ‘hydrolyzable’ because they can be easily broken down via acid hydrolysis (stomach acid). The hydrolyzable tannins are soluble in both alcohol and water. The two subgroups are the ellagitannins and the gallotannins.

56. High concentrations of ___________________________ are found in Raspberry leaf, Strawberry leaf, and Pomegranate fruit. These polyphenols are antioxidant, anti-inflammatory, and anticarcinogenic. Numerous studies have found that the ellagitannins and their metabolites in Pomegranate (e.g., punicalin, punicalagin, tellimagrandin, and corilagin) have considerable activity against various types of cancer cells.

57. Other sources of ellagitannins include grapes, green and black teas, wild geranium (Geranium maculatum) root, and white oak bark (contains a complex mixture of ellagitannins and gallotannins: astringent, bacteriostatic, and anti-inflammatory). Ellagitannins from walnut have demonstrated potent antioxidant and antifungal properties. The leaf of this tree contains about 10% ellagitannins and is used __________________ for eczema and skin disorders.

58. Gallotannins are represented by compounds such as hamamelitannin, the major constituent in Witch Hazel bark, where it occurs along with condensed tannins and other polyphenolic compounds. Witch Hazel is a classic old-time ___________________.

59. The astringent substance known as ‘____________________’ contains a mixture of gallotannins. Oak galls from Quercus infectoria are the major commercial source. Extracts of Q. infectoria have strong antibacterial activity and are even effective against drug-resistant Staphylococcus aureus (MRSA) and enterohemorrhagic Escherichia coli. Like most polyphenols, they also have antioxidant and anti-inflammatory properties.

Proanthocyanidins (glycosides are called proanthocyanins): OPCs (oligomeric proanthocyanidins) or condensed tannins – as opposed to hydrolyzable tannins – these fairly sturdy phenolic compounds are made up of two or more linked flavanol units. The smaller ones (the OPCs) are soluble in hot water; but they can also continue the polymerization process to make larger and larger tannins, which lose their ability to dissolve in water when they reach a certain size. These compounds are colorless.

60. Two or three linked catechin, epicatechin, or delphinidin units, and/or their gallate esters, make up the various ___________________________ or prodelphinidin dimers or trimers. Grape seed or Pine bark extracts (e.g., Pycnogenol®) contain mainly procyanidin dimers B1 and B2, and the trimer C1, along with catechin, epicatechin, and gallic acid.
61. Green tea, hawthorn, and ginkgo are rich sources of OPCs. In general, the OPCs have antioxidant, anti-inflammatory, anticancer, cardiotonic, astringent, and antimicrobial properties. In Cranberry (*Vaccinium macrocarpon*) they have exhibited beneficial effects on LDL oxidation, platelet aggregation, inflammation, thrombosis, and blood pressure regulation. By preventing bacteria from adhering to the __________ lining the interior of the bladder, the OPCs help to clear the infection (urinary tract infections) and prevent recurrences.

62. Theaflavins and thearubigins: When tea leaves are fermented, some of the OPCs are changed into theaflavins (flavan-3-ol dimers which have undergone oxidation). Theaflavins are orange antioxidant pigments which may help to prevent cardiovascular disease, cancer, and __________ aging. They also have strong antimicrobial properties. The closely-related thearubigins are complex, variable polymers of oxidized flavan-3-ol monomers; these are the reddish-brown pigments found in some fermented teas. The theaflavins appear to be more physiologically active than the thearubigins.

In the isoflavonoids, the ‘B’ ring has migrated to position 3 of the central ring. The relatively small structural difference is reflected in their name, which means ‘isomers of flavones.’ Isoflavonoids occur primarily in the legumes (Fabaceae family), where they act as chemoattractants for nitrogen-fixing bacteria in the soil. Additionally, they are antifungal phytoalexins, and some serve as insecticides because their steroid-mimicking structures can disrupt growth and development in insects.

Isoflavonoids and their derivatives, many of which are biologically active, are often referred to as phytoestrogens.

63. The richest sources of isoflavones include Red Clover (*Trifolium pratense*) leaves and sprouts (biochanin A, formononetin), Soybeans and sprouts (genistein, daidzein, and glycitein), and Kudzu (*Pueraria lobata*) root (puerarin, daidzein). Once isoflavones are ingested, the colon microflora metabolize biochanin A into genistein and formononetin into daidzein. In about one third of the population, daidzein is further metabolized to become a molecule called equol. This compound has a strong affinity for hormone receptors and demonstrates considerable antioxidant and __________ activity.

One study reports that women who produce equol have hormonal profiles associated with a lower risk of breast cancer: lower concentrations of androstenedione, dehydroepiandrosterone (DHEA), estrone, cortisol, and testosterone; along with higher concentrations of sex hormone binding globulin (SHBG). Differences in the ability to produce equol may help to explain some of the mixed results from studies on the effects of isoflavones in humans.

64. The effects of phytoestrogens vary depending on the levels of endogenous estrogens in the body. If endogenous estrogens are low, these compounds can have a mild estrogen-enhancing effect. But if endogenous estrogens are high, they can have an anti-estrogenic effect. Many people think of them as SERMs (selective estrogen receptor modulators) because of this __________ action.
65. Benzofurans are rather uncommon compounds. One benzofuran constituent encountered in herbal medicine is usnic acid, which occurs in several species of ___________ (Old Man’s Beard) and other lichens. Usnic acid has antifungal, antiviral, antiprotozoal, anti-inflammatory, and antitumor properties. This low-polarity constituent has very little solubility in water, and is best extracted with hot ethanol. **Ethanol is very flammable - do not attempt this in the kitchen. Buy the extract or take a hot plate outside!**

66. Chromones are rarely encountered in medicinal plants. In the Ayurvedic herb Khella (Ammi visnaga), khellin, visnagin, and related chromones contribute significantly to its actions as an antispasmodic, vasodilator, cardiovascular tonic, a bronchodilator for ________________, and an antitussive that works via activity in the central nervous system.

Quinones are defined by a six-carbon ring bearing two opposite ketone groups (para-ketones). In medicinal plants, we find three subtypes: the isoprenoid benzoquinones, the naphthoquinones, and the anthraquinones (anthraquinone glycosides).

67. Isoprenoid benzoquinones contain one quinone ring and an oil-soluble ‘isoprenoid’ tail. One example is ubiquinone, more commonly known as coenzyme Q10 (Co-Q10). Without this all-important compound the electron transport chain of aerobic ________________ respiration could not function. Therefore the compound is universal in plant and animal cells; hence the name ubiquinone: the ubiquitous quinone.

68. Naphthoquinones contain two fused rings. They are brownish-orange pigments with ____________ properties. A prominent example is juglone, found along with the closely-related compound plumbagin, in the green outer hulls of walnuts (Juglans spp.). When applied topically, these compounds have strong antifungal, antiviral, and antibacterial effects; however, the isolated naphthoquinones have the potential to damage keratinocytes if used in excess.

Black walnut (Juglans nigra): The green unripe fruit should be harvested when they are about 1/2 of their full, mature size - highest in active phenolic compounds (principally juglone) at this stage. Peel the entire hull from around the embryonic nut and immediately immerse them in a menstruum consisting of a blend of 40% ethanol (80 proof vodka will work), 30% vegetable glycerin, and 30% apple cider vinegar. The vinegar slows the enzymatic breakdown of juglone, which is a major active ingredient, providing the highest quality extract with good stability. Use the herb tincture in a dose of 1/2 to 1 teaspoon in a little water, several times a day. I have found it especially useful for relieving the symptoms of diarrhea due to giardia infection. Think of it for Candidiasis, athlete’s foot, and ringworm. Take 1/2 teaspoon in a little water or tea twice daily as a preventative for bacterial infections when traveling. - https://www.christopherhobbs.com/herb-walk/black-walnut/

69. A similar molecule, lawsone, is the skin-coloring pigment in Henna (Lawsonia inermis). Aside from its cosmetic applications, Henna is a traditional herbal remedy used in Ayurvedic medicine to kill ________________ and for fungal infections of the skin. Lawsone exhibits antioxidant and immunomodulatory properties and has many of the same antimicrobial and antifungal effects as juglone.
70. **Lapachol**, a naphthoquinone from ____________ (*Taheebo: Tabebuia spp.*), is an *immunostimulant at low doses* and a *cytotoxic anti-tumor compound at higher doses*. It also has topical anti-inflammatory and analgesic properties and it shows some antifungal activity against *Candida albicans*.

71. A subgroup of the naphthoquinones, the **isoprenoid naphthoquinones**, includes phylloquinone (vitamin K1). This compound’s name means ‘leaf quinone.’ Vitamin K2, or menaquinone, is synthesized by ________ bacteria and is not a phytochemical per se. The vitamins K are oil-soluble compounds necessary for prothrombin synthesis (required for normal blood clotting) and osteocalcin function (in bone formation).

72. **Anthraquinones** contain three fused rings, with the quinone in the middle. They are distinctly reddish-orange compounds, and frequently occur in the form of *water-soluble glycosides*. These familiar molecules have the undisputed physiological effect of stimulating peristalsis in the bowels. Anthraquinones are found in classic ‘_____________’ herbs such as Senna (the sennosides), Cascara (the cascarosides), Aloe (aloe-emin), and the **milder** Yellow Dock (emodin, chrysophanol, and rhein).

Quinones as isolated compounds have been associated with the development of cancer, because they are reactive and can bind to the DNA. This is not known to happen with the commonly-used herbs, although avoiding overdoses of such plants makes cautious sense.

![Yellow dock root](image)

**Yellow dock root:** A gentle laxative herb due to synergy in the plant, a good herb for constipation in pregnant women. It is also nutrient and mineral rich and is often used as part of herbal blends to increase iron. A simple iron tonic: Equal amounts of Dandelion root, Burdock root and Yellow dock root: simple decoction, transfer to jar and add molasses, deliver in a cup of nettles. Make enough for 3-4 days and store in refrigerator. Don’t eat the leaves! They are high in oxalic acids.

73. **Hypericin and pseudohypericin**, the compounds that give a *red hue* to *St. John’s Wort oil*, are known as a bianthraquinones or naphthodianthrones. **Hypericin** is a __________ contributor to the antiviral and antidepressant activity of Hypericum, and, being a UV-activated compound, is also responsible for the cases of photosensitivity that have been reported by a small percentage of users.

Phloroglucinol Derivatives don’t seem to fit into other categories well, but they share the feature of being derived from a biosynthetic precursor called phloroglucinol. These compounds, sometimes called phenolic ketones, include **hyperforin** from *St. John’s Wort* (an antidepressant synergist), the **cannabinoids** (e.g., the psychoactive, bronchodilatory, and antiemetic THC-type compounds from *Cannabis*), and the bitter antioxidant and antibacterial molecules found in *Hops strobiles*, *humulone* and *lupulone*. 
74. **Resinous (very low-polarity) cannabinoids** (e.g., tetrahydrocannabinol and cannabidiol) are the subject of much current research. Earlier we discussed the fact that various types of human cells have _____________ receptors which interact with our endogenous cannabinoid compound, anandamide, as well as with the omega-3 fatty acids and the isobutylamides from Echinacea. This system is involved in the regulation of inflammatory processes, neuropathic pain perception, muscle relaxation, and the hunger/satiety axis. It is well-established that the cannabinoids are anti-emetic, making Cannabis a useful adjunct treatment for chemotherapy; it can also be helpful for cancer-associated pain and cachexia. Although this herb can be very useful for some patients, **people with bipolar disorder or schizophrenia may not tolerate it well.**

75. **Phenolic Resins and Propolis:** The _________ from various *Populus spp.* (e.g., Cottonwood) buds, are composed of complex mixtures of low-polarity phenolic aglycones. Bees collect this material in the early spring and use it to make Propolis. Propolis means ‘before the city,’ reflecting the fact that the bees use it to line entrances to their hives and to fill in cracks and holes. This substance is a strong antimicrobial that helps to protect the colony from infection.

Beekeepers sometimes find dead mice inside a hive; since the bees can’t physically remove such intruders, they use Propolis to embalm them and prevent infection from decay. The phenolic resins of Propolis were also employed in ancient times to preserve mummies, and as glues and varnishes. Today we harvest the antimicrobial powers of phenolic-rich Propolis in products such as gum treatments, throat sprays, and pastilles. Research has also identified immunomodulatory, antimutagenic, anticarcinogenic, anti-inflammatory, and anti-ulcer activities in Propolis. Be aware, however, that a small percentage of people will experience allergic contact dermatitis from exposure to this substance.

END OF CHAPTER EIGHT TEST