

# **Rheumatoid Arthritis and Osteoarthritis**

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# Arthritis and Musculoskeletal Disorders

- Arthritis- wide spectrum of disorders, all characterized by inflammation and tissue damage at the joints.
- Includes rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, osteoarthritis, fibrositic disorders, and more.
- Osteoarthritis is most prevalent (10% of our population is impacted).
- Ranks second only to cardiovascular disease in causing chronic disability due to pain, limitation in motion, deformity and progressive deterioration.

# Arthritis and Musculoskeletal Disorders

- The immune response plays a significant role in producing local inflammation and tissue damage. Macrophages engulf and process antigens that are then presented to T lymphocytes where they stimulate the production of activated T cells.
- The activated T cells produce cytotoxins and cytokines, which stimulate the inflammatory processes and attract cells to areas of inflammation.
- Vasoactive substances (e.g. histamine, kinins, and PGs are released at the site of inflammation) increasing blood flow and permeability of blood vessels. These cause edema, warmth, erythema and pain associated with inflamed joints.

# Arthritis and Musculoskeletal Disorders

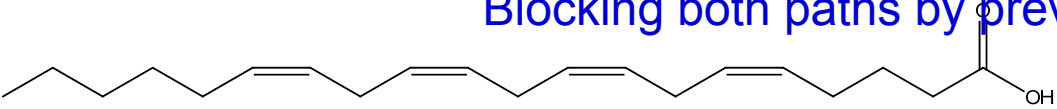
- Drug therapy includes the administration of salicylates or other nonsteroidal anti-inflammatory drugs (NSAIDs).
- These reduce inflammation, confer some degree of analgesia, maintain joint mobility and reduce pain and mitigate against deformity in the short-term.
- NSAIDs reduce PG biosynthesis through inhibition of cyclooxygenase.

From Robbins and Tyler:  
 Pathway of Biosynthesis  
 for Eicosanoids and sites  
 Inhibition for  
 anti-inflammatory drugs:

Cellular membrane (phospholipids

Phospholipase A2

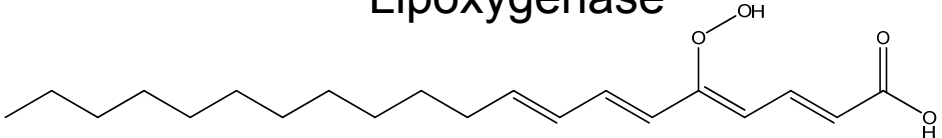
Glucocorticoids act/block here,  
 Blocking both paths by preventing



Arachidonic acid

Membrane release of Arach. acid

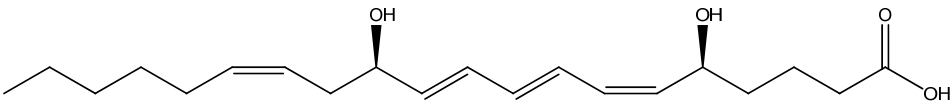
Lipoxygenase



5-HPETE

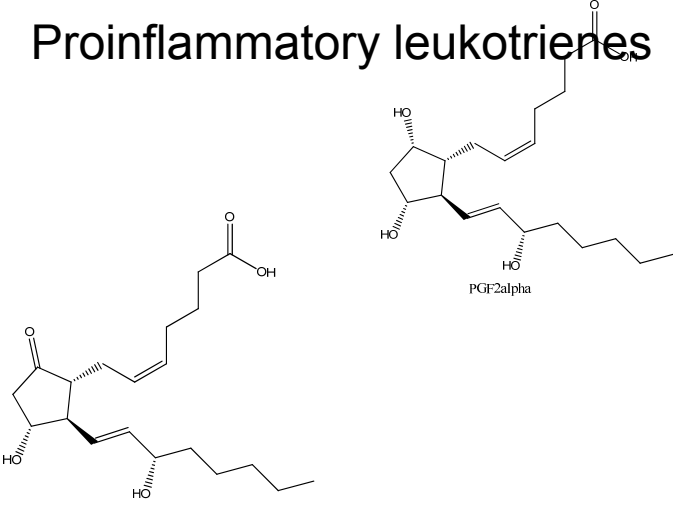
Cyclooxygenase

Willow Bark (salicin NSAIDs  
 Act/Block here, thus reducing  
 PGs by inhibition of this enzyme



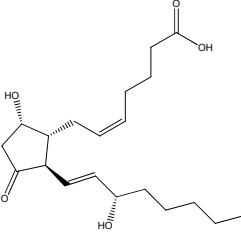
LEUKOTRIENE B4

Proinflammatory leukotrienes



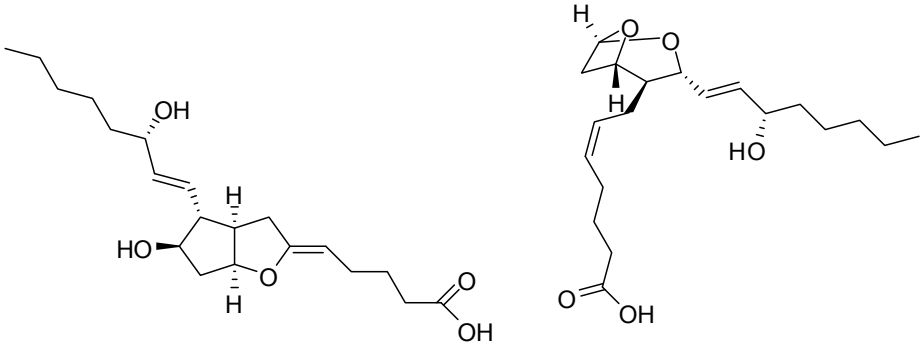
Prostaglandins PGE2

PGF2alpha



PGD2

Cyclic endoperoxides--- PGs



Prostacyclin

Thromboxane A2

# Dietary Products Used in Rheumatoid Arthritis and Osteoarthritis

- *Bowellia* (*Boswellia serrata*)
- Cetyl myristolteate (CMO)
- Chondroitin sulfate
- Devils claw (*Harpagophytum procumbens*)
- Glucosamine
- Green-lipped mussel (*Perna canaliculus*)
- Hydrolyzed collagen protein (HCP)
- Gelatin
- Methylsulfonylmethane (MSM)
- Sea cucumber (*Stichopus japonicus*)
- Willow bark tea (historical)

# Bowellia (*Boswellia serrata*)

- Also known as Frankincense, important as an incense and spice-used in Arminian churches and in Ayurvedic medicinal
- Known as an anti-inflammatory
- Bioactive compounds are: boswellic acids which have been shown to be specific, noncompetitive nonredox inhibitors of 5-lipoxygenase (key enzyme involved in leukotriene biosynthesis)
- The leukotrienes appear to promote inflammatory conditions
- Used in the dietary supplement industry mainly for inflammation, joint pain and sports injuries



# Rheumatoid Arthritis and Osteoarthritis Boswella Clinical:

From Sander et al 1998:

- Multicenter, controlled clinical 18 patients given boswellia. Dosage @ 3,600mg/day) and 19 given a placebo plus other prior therapy which may have been NSAIDs (nonsteroidal anti-inflammatory drugs).
- Patients measured at 6 and 12 weeks- Ritchies Index for swelling and pain, and other parameters: NSD in subjective, clinical or lab analysis of any parameters between both groups.

From Kulkarni et al. 1991, 1992:

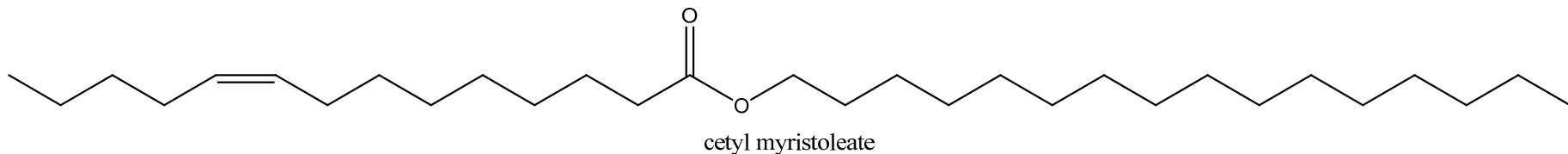
- Conducted two clinicals involving formulation with boswellia in treatment of osteoarthritis. Outcome positive but not known whether boswellia or other herbs in mix were responsible for that change.

# Bowellia (Talbot and Hughes)

- Dose is 450-1,200mg/day 3x.
- Standardized extracts are recommended (30-60% boswellic acid)
- No reports of serious adverse effects, but mild to transitory gastrointestinal upset reported (Kimmatkar et al. 2003)

# Cetyl Myristoleate

- CM or CMO is cis-9-cetyl myristoleate (cetylated fatty acids (CFAs) primarily myristoleic acid (14:1) and a long chain alcohol, cetyl alcohol.
- Found in nuts, olive oil, vegetables and dairy products, fat and lard, and marine organisms.
- Used in the dietary supplement industry as a general anti-inflammatory agent.
- Dietary ingestion of CM by people with osteoarthritis has provided some relief from pain, stiffness, and mobility, while underlying mechanism(s) is unknown.
- CM reported to act as a surfactant to 'lubricate joints'

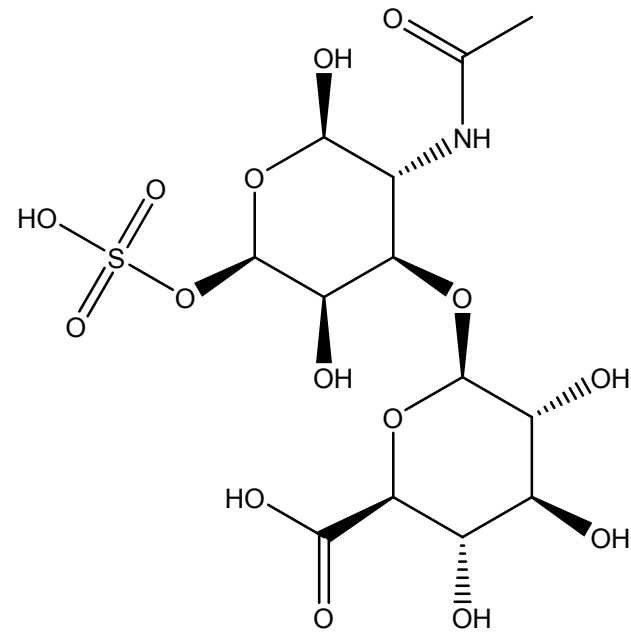


# Cetyl Myristoleate, con't

- Myristoleic acid inhibits 5-lipoxygenase in tissue
- CM may regulate androgen activity
- Studied to date only as a pain reliever in mild to moderate case of osteoarthritis.
- Epidemiological and clinical evidence suggests that patients with both rheumatoid arthritis and osteoarthritis benefit from consuming higher levels of dietary eicosapentaenoic and docosahexaenoic acids (e.g. in fatty fish that are rich in  $\omega$ -3 polyunsaturated fatty acids)
- Cetylated monounsaturated fatty acids have provided protection against arthritis in rats, increased knee motion and reduced pain in people with osteoarthritis.

# Chondroitin sulfate

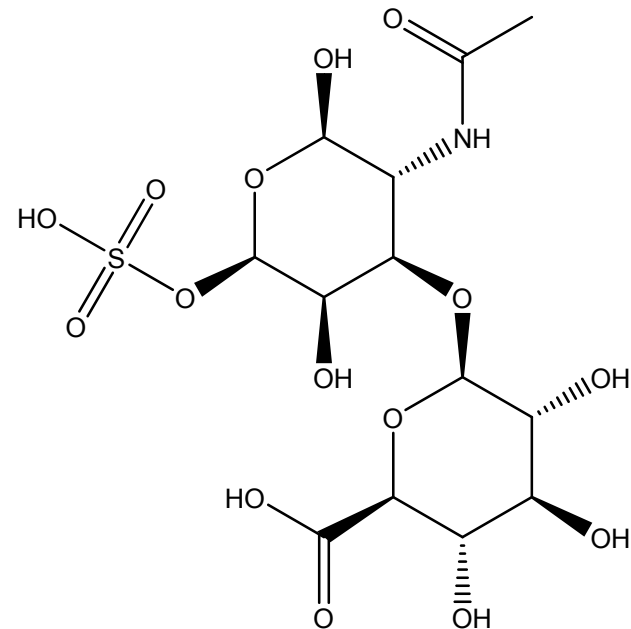
- Long chains of polysaccharides.
- Building blocks of proteoglycans, which are used to form connective tissue such as cartilage.
- Related to another sugar derivative, glucosamine- used for same application.
- Primary source is animal cartilage (trachea of cows)
- Marketed to consumers with joint pain and aches.
- Often marketed now with glucosamine
- Concept is that dietary ingestion of chondroitin sulfate provides raw materials for cartilage repair.
- Second concept is that it blocks enzymatic activity that breaks down cartilage.
- Studies show it relieves pain and stiffness but only in osteoarthritis
- Absorption was under debate but @ 10-20% of product is absorbed intact, while additional is presumed to be digested and absorbed in parts.
- Science



Chondroitin sulfate

# Chondroitin sulfate, cont

- Pain relieving effects of chondroitin have compared favorably to other NSAIDs such as naproxen and ibuprofen.
- Chondroitin appears to take a longer time to provide relief but lasts longer than the NSAIDs.
- Some evidence shows it retards the progressio of cartilage degradation
- Topical also effective? Not sure as in the study other ingredients (e.g. camphor) were included too.



Chondroitin sulfate

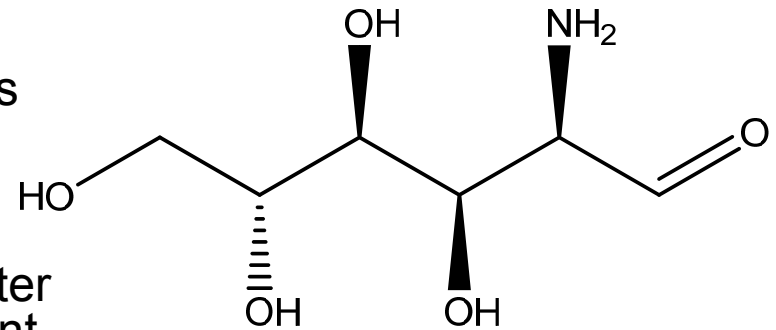
# Devils claw (*Harpagophytum procumbens* and *H. zeyheri*)

- Medicinal value of devils claw long known by the indigenous Nama, San, and Khoi peoples of southern Africa.
- First recognized by the 'west' by a German farmer emigrated to Namibia in early 1990's.
- As phytomedicine, the official drug, *Harpagophytum* comes from the tubers of this plant
- Active compound is harpagoside, extracted using solvent extractions, at ca. 2-3% dry wt.
- *H. zeyheri* also contains iridoid 8-p-coumaroyl-harpagide (PCHG).
- Medicinal applications for painful arteriosclerosis, gastro-intestinal complaints, loss of appetite, diabetes, hepatitis, neuralgia. Also used to treat spasmodic blood pressure, found to improve the liver, gallbladder, and treating kidney diseases and senility.
  
- The drug has anti-inflammatory properties and shows analgesic effects.
- Appears effective for joint, low back and arthritis pain



- Appears very effective for joint health, and marketed with 'claims' of protecting joints and joint cartilage from injury, alleviating stiffness and pain in osteoarthritis and reducing inflammation.
- Glucosamine is an aminopolysaccharide
- Its concentrated in joint cartilage, where it is incorporated into longer chains as glycosaminglycans and larger ones, proteoglycans.
- Proteoglycans function in part to attract water into joint space, lubrication during movement.
- Popular dietary supplement as glucosamine sulfate, glucosamine hydrochloride and N-actylglucosamine.
- Chondroitin sulfate often combined with glucosamine, but no evidence showing the combination is more effective.
- Usually takes 1-3 months to show effects
- Underlying theory proposes that the glucosamine is delivered to the joint space and incorporated into proteoglycans of joint cartilage to maintain structure, repair damage.
- Glucosamine may stimulate new cartilage cells to produce new cartilage matrix materials.
- Appears stronger evidence with mild-to-moderate severity.

# Glucosamine



Glucosamine

# Green-lipped mussel (*Perna canaliculus*)

- Also sold as a dietary supplement to relieve arthritis and joint pain and promoting the building of reconnectorive tissue, tendons, ligaments and cartilage as it too contains high concentrations and diverse glycosaminoglycans.
- Also contains omega fatty acids
- Science is limited. Studies appear potentially promising as to arthritis and joint pain and stiffness, moderate as to effectiveness in inflammatory conditions and in promoting of post-exercise recovery. Yet several studies showed no benefit to that of matching NSAIDs.

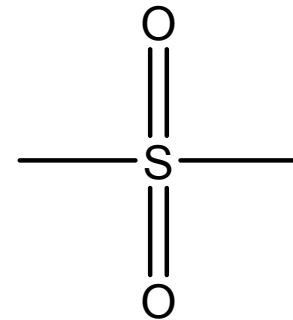
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# Hydrolyzed collagen protein (HCP) or Gelatin

- Chief structural protein that makes up the connective tissue.
- HCP is a modified form of the protein enzymatically broken down.
- The hydrolysis process used prevents the collagen to form a gel or aggregate together and thus allows it to the protein to be mixed/blended into dairy products and some presume this results in increased absorption of the amino acids once ingested.
- HCP is sold and used then as general protein source in bodybuilding products as it is inexpensive but not shown to be effective.
- In contrast the use of HCP to promote joint health, cartilage and bone health and/or in post-injury treatment of athletes from sports-related injury looks a bit more promising.
- HCP is less expensive than glucosamine and chondroitin, but the level of science as to its efficacy is also not there.
- HCP is not considered a complete nor good protein source and is low in the sulfur containing amino acids such as cysteine and methionine.
- HCP is rich in glycine, proline, hydroxyproline, lysine, and hydroxylysine.
- Claims appear a bit speculative.

# Methylsulfonylmethane (MSM)

- As a sulfur supplement, has been called vitamin U, and is a metabolite from the solvent that also has been shown to have anti-inflammatory and analgesic properties, DMSO, or dimethylsulfoxide.
- Does it really supply the body with sulfur used in skin, hair, tendon and cartilage health?
- As a dietary supplement in joint health, it is presumed to provide sulfur in those connective tissues impacted by arthritis.
- Often used in combination with glucosamine sulfate and chondroitin sulfate products, little clinical support is available for efficacy of use.



Methylsulfonylmethane

## Sea cucumber (*Stichopus japonicus*)

- Sold and marketed as a dietary supplement for joint pain and fibromyalgia, little evidence is available for its efficacy.
- Related to starfish, this sea animal contains chondroitin, glycosaminoglycan and other mucopolysaccharides, hence its assumption of efficacy and marketability.
- Also harvested as a delicacy in Asia, its sustainability is an issue.

# Willow Bark (*Salix* spp.)

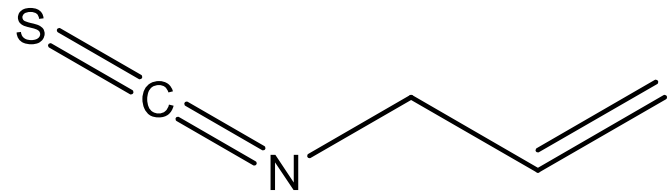
- *Salix alba*, *S. purpurea* and *S. fragilis*
- Bark of the tree
- Salicin, or chemically salicyl alcohol glycoside, fragilin, tremulacine
- These other glycosides are heat labile and converted to salicin when dried at high temps.
- All the phenolic glycosides are prodrugs, and all converted to the active compound, salicylic acid in the intestinal tract and liver.
- Willow bark shows anti-inflammatory, analgesic, and antipyretic effects by inhibition of cyclooxygenase and PG biosynthesis.
- Side effects – gastrointestinal upset caused by tannins

# Rubefacients (Agents reducing redness and irritation)

- External analgesics of plant origin are widely used as dietary supplements and/or over the counter counter irritants.
- External analgesics are used to alleviate pain resulting from trauma to muscle injuries from sports, working etc. and to treat pain from arthritis.
- Estimated that >40% of adults use such products.
- Efficacy appears to be related to their use when applied to the skin over or near site of underlying pain, they product a mild local irritation that stimulate delta A nerve fibers which act to counter the dull throbbing pain transmitted by the type C nerve fibers which are involved in the perception of pain.
- Different counterirritants are classified by their physiological action. Those producing dilation of the cutaneous vasculature and subsequent reddening of the skin- rubefacients. Localized warming and redness causes person to ignore the other pain. Often these agents are stronger, and more potent and have potential to cause blistering and erythema- slight burning.
- A second type causes a cooling sensation on the skin and depress the sensory cutaneous receptors and act as local anesthetics.
- A third type includes agents that produce irritation and warmth to the skin but without producing the rubefaction.

# Rubefacients (Agents reducing redness and irritation)

- Volatile mustard oil
- From dried ripe seeds of the black mustard (*Brassica nigra*);
- Seed is ground, macerated in water, the enzyme, myrosin then converts the glycoside sinigrin to allyl isothiocyanate. This volatile is then purified by distillation and included into several counterirritants for external preparations.
- Or a poultice is prepared using the seeds and flour of mustard.
- FDA approves its use as safe and effective counterirritant

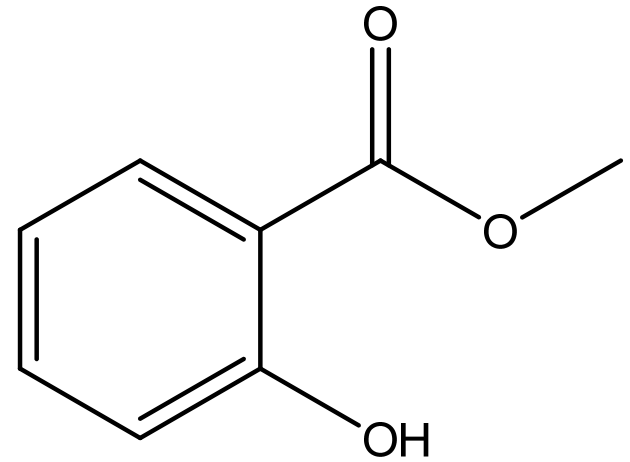


Allyl isothiocyanate

# Rubefaciants (Agents reducing redness and irritation, cont)

## Methyl salicylate

- From EO of the wintergreen, *Gaultheria procumbens* or bark of sweet birch (*Betula lenta*): wintergreen oil or sweet birch oil.
- Can be natural or synthetic.
- Methyl salicylate is topically used as a counterirritant.
- There is concern as to potential toxicity.



methyl salicylate

# Rubefaciants (Agents reducing redness and irritation, cont)

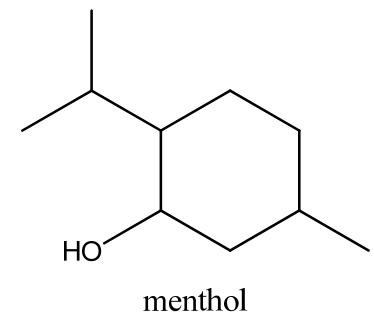
## Turpentine Oil

- From EO of *Pinus palustris*.
- Spirit of Turpentine
- Long history of use as a counterirritant.

# Refrigerants (Agents inducing a cooling sensation)

## Menthol

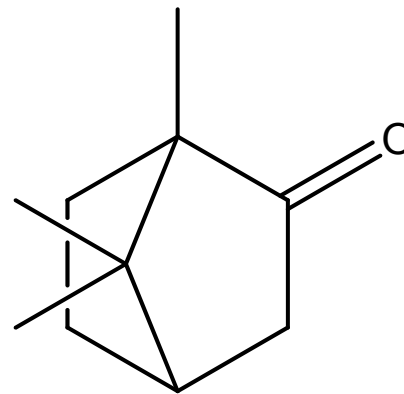
- From EO of mint (*Mentha* spp., usually from *M. arvensis*).
- Topically applied and used in higher concentrations is a counterirritant.
- Menthol has little effect on histamine-induced itch, nor does it affect pain sensation as a local anesthetic.



# Refrigerants (Agents inducing a cooling sensation, cont)

## Camphor

- From EO of *Cinnamomum camphora*.
- Topically used as a counterirritant, depresses the cutaneous receptors providing local analgesic, local anesthetic actions.

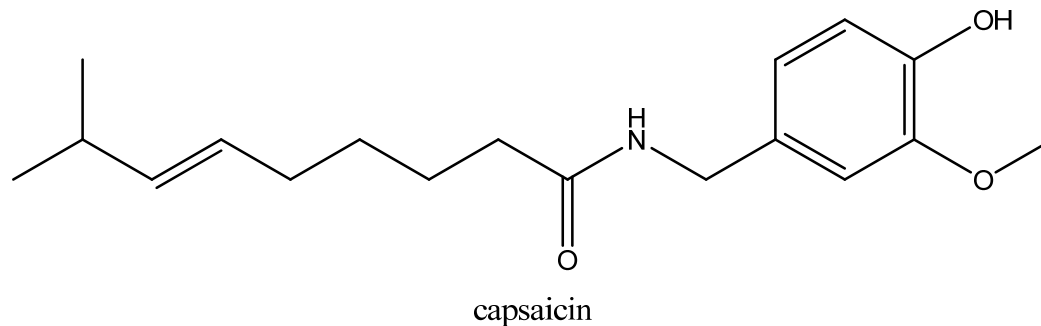


camphor

# Refrigerants (Agents inducing a cooling sensation, cont)

## The Capsainoids

- From *Capsicum* spp., such capsaicin creams provide counterirritant activity without rubefaction.





# Dietary Products Used for Stimulation or Regulation of the Immune System

- Astragalus
- Cats Claw (*Uncaria tomentosa* and *Uncaria Guianensis*)\*  
Contains pentacyclic and/or tetracyclic oxindole alkaloids
- Sulfasalazine
- Hydroxychloroquine
- Colostrum
- *Echinacea* spp.
  - *E. purpurea*
  - *E. angustifolia*
  - *E. pallida*
- *Glutamine*
- *Goldenseal (Hydrastis canadensis)*
- *Perilla Seed oil*
- *Bovine and/or Shark cartilage*
- *Ginseng*
- *Ashwagandha*
- *Feverfew*
- *Ginkgo*

\*Also for osteoarthritis and rheumatoid arthritis