A bridge from traditional medicine into modern medicine

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Devil’s Claw

• Name: Harpagophytum procumbens (Burch.) DC. ex Meissn. (Pedaliaceae)

• Part(s) Used: Secondary root tuber

• The iridoid constituents are thought to be responsible for the reputed anti-inflammatory activity of devil’s claw

• Pharmacopoeial and Other Monographs:
  – BHC 1992(G6)
  – BHMA 2003(G66)
  – BHP 1996(G9)
  – BP 2007(G84)
  – Complete German Commission E(G3)
  – ESCOP 2003(G76)
  – Martindale 35th edition(G85)
  – Ph Eur 2007(G81)
Constituents:
- Diterpenes: \(8,11,13\)-totaratriene-12,13-diol and \(8,11,13\)-abietatrien-12-ol.
- Iridoids Harpagoside (1–3%), harpagide, 8-p-coumaroylharpagide, 8-feruloylharpagide, 8-cinnamylmyoporoside, 60-O-p-cumaroylharpagide, 60-p-coumaroylprocumbide, and pagoside.
- Phenylpropanoids: Acteoside and isoacteoside, 6-O-acetylatedacteoside, (4–6) 2,6-O-diacetylatedacteoside.
- Other constituents: Amino acids, flavonoids (e.g. kaempferol, luteolin), triterpenoids, sterols

The harpagoside content of commercial extracts of H. procumbens has been reported to range from 0.8–2.3 %
• **Traditionally**, it has been used as a stomachic and a bitter tonic, and for arthritis, gout, myalgia.

• **Modern use** of devil's claw is focused on its use in the treatment of rheumatic and arthritic conditions, and low back pain.

• Painful arthrosis and tendonitis: 1.5–3 g dried tuber as a decoction, three times daily (equivalent to less than 30 mg up to 100 mg harpagoside daily)

• Loss of appetite or dyspepsia: 0.5 g as a decoction, three times daily

**Ethnopharmacology:**

• Animal studies of the anti-inflammatory and analgesic activities of devil's claw have reported conflicting results.

• Pretreatment with a dried aqueous extract of devil's claw root at doses of 100 mg/kg and above, administered intraperitoneally, resulted in **peripheral analgesic activity** demonstrated by a significant reduction in the number of writhings induced by acetic acid in mice.(16) However, no effect was observed in the hotplate test, indicating a lack of **central analgesic** activity with devil's claw extract.

• However, dried aqueous extract of devil's claw administered by intraperitoneal injection demonstrated significant activity in the carrageenan-induced oedema test in rats, an acute model of inflammation.
Mechanism of action

- In vitro, devil's claw (100 mg/mL) had no significant effect on prostaglandin (PG) synthetase activity, whereas indometacin (316 mg/mL) and aspirin (437 mg/mL) caused 50% inhibition of this enzyme.
- In other in vitro studies in human whole blood samples, devil's claw extracts and fractions of extracts were tested for their effects on thromboxane B2 (TXB2) and leukotriene (LT) biosynthesis.
- TXB2 is an end-product of arachidonic acid metabolism by the cyclooxygenase 1 (COX-1) pathway. Inhibition appeared to be dependent on the harpagoside content of the extracts or fractions.
- An aqueous extract of H. procumbens inhibited lipopolysaccharide-induced enhancement of cyclooxygenase-2 activity, resulting in suppression of PGE2 synthesis in in-vitro experiments using the mouse fibroblast cell line L929.
- In the same system, the extract inhibited inducible nitric oxide synthase (iNOS) mRNA expression, resulting in suppression of nitric oxide production.
- Harpagoside (100 mmol/L), but not harpagide (100 mmol/L), inhibited calcium stimulated release of TXB2 from human platelets with no inhibitory effect on calcium stimulated release of PGE2 and LTC4 from mouse peritoneal macrophages.
- (In inflammatory diseases, there is increased production of cytokines such as IL-1b and TNF-a, which results in an increased production of MMPs which breakdown the extracellular cartilage matrix.)
- An ethanol extract of H. procumbens significantly reduced IL-1b-induced production of several matrix metalloproteinase enzymes (MMPs) in human chondrocytes.
- Other activities Crude methanolic extracts of devil's claw have been shown to be cardioactive in vitro and in vivo in animals. In isolated rabbit heart, low concentrations of a crude methanolic extract had mild negative chronotropic and positive inotropic effects whereas high concentrations caused a marked negative inotropic effect with reduction in coronary blood flow.
In mice, a methanol extract of H. procumbens root tubers applied topically to shaven skin 30 minutes before application of phorbol-13-acetate (TPA), a stimulator of COX-2 expression, led to a significant reduction in COX-2 protein when assessed four hours after TPA administration.

Pharmacodynamics

A study involving healthy volunteers investigated the effects on eicosanoid production of orally administered devil's claw (four 500-mg capsules of powder, containing 3% glucoiridoids, daily for 21 days). No statistically significant differences on PGE2, TXB2, 6-keto-PGF1a and LTB4 were observed following the period of devil's claw administration, compared with baseline values.

There was also evidence (from one trial for each) that the same extract administered orally at a dose equivalent to harpagoside 100 mg daily for four weeks was superior to placebo, and at a dose equivalent to harpagoside 60 mg daily for six weeks was not inferior to rofecoxib 12.5 mg daily, in reducing pain in patients with acute episodes of chronic non-specific low-back pain.
A randomised, double-blind, pilot trial in which 88 participants with acute exacerbations of low back pain received an aqueous extract of devil's claw (Doloteffin), or rofecoxib (Vioxx) for six weeks offered participants continuing treatment with devil's claw aqueous extract two tablets three times daily for up to one year after the six-week pilot study. There were no convincing differences between the two groups (i.e. those who previously received devil's claw and those who received rofecoxib).

Side-effects, Toxicity

While there are no documented reports of gastrointestinal bleeding or peptic ulcer associated with the use of devil's claw, the latter statement requires confirmation. Use of devil's claw in gastric and duodenal ulcer is contraindicated, although this appears to be because of the drug's bitter properties.

Randomised, placebo-controlled trials involving patients with rheumatic and arthritic conditions who have received devil's claw extracts or powdered drug at approximately recommended doses for four weeks have reported mild, transient gastrointestinal symptoms (such as diarrhoea, flatulence) in a small proportion (less than 10%) of devil's claw recipients. No serious adverse events were reported, although one patient withdrew from one study because of tachycardia.

Acute and subacute toxicity tests in rodents have demonstrated low toxicity of devil's claw extracts.
Contra-indications, Warnings

- However, on the basis of pharmacological evidence of devil’s claw’s cardioactivity, the possibility of excessive doses interfering with existing treatment for cardiac disorders or with hypo/hypertensive therapy should be considered. Inhibitory effects on certain cytochrome P450 (CYP) drug metabolising enzymes have been documented for a devil’s claw root extract.

- Pregnancy: It has been stated that devil’s claw has oxytocic properties so its use should be avoided during these periods.

Avocado (Persea Americana)


Synonyms/Common Names/Related Substances:
- Abokado, aguacate,ahuacate, ahucatat, alligator pear, avocado pear, Avocado, Persea americana, americana var: drymifolia Blake, Persea gratissima, Persea leiocyna, Persea rubigna var: guatar Persea persica, Laurus persica.
- Combination product examples: Avocado/soybean unsaponifiables (ASU), Piascledine®, Regivid

Clinical Bottom Line/Effectiveness

Brief Background:
- Avocados are fruits, not vegetables, belonging to the genus Persea and the Lauraceae family. Avocados are a nutritious source of potassium, containing 60% more potassium than bananas; they are also sodium- and cholesterol-free. An avocado has a higher fat content (5g per serving) than other fruit, but the fat is monounsaturated fat, which is considered healthy when consumed in moderation in the human diet. Diets rich in monounsaturated fatty acids can reduce serum total cholesterol and increase the ratio of high-density lipoprotein (HDL) to low-density lipoprotein (LDL). Several studies have reported that diets rich in avocado may reduce plasma lipid levels. Avocado is also a rich source of beta-sitosterol, which is believed to have cholesterol-lowering effects as well as anti-cancer effects.
- Avocado is also used for osteoarthritis. Studies suggest avocado and other soybean extracts stimulate collagen growth and reduce the use of NSAIDs. Patients with osteoarthritis of the hip appear to gain a greater benefit.
- The most promising use for avocado is in a combination product, Avocado/soybean unsaponifiables (ASU), which is a combination of avocado oil and soybean oil. It has been shown in several good human trials that ASU is effective in osteoarthritis. This is supported by in vitro studies that have demonstrated that ASU can reduce cytokines, prostaglandin E2, metalloproteinases and pro-inflammatory mediators produced by human chondrocytes.
**Folkloric Precedent:**
- In folk medicine, mashed raw avocado has been rubbed onto the skin for treatment of psoriasis; the oil is patented for some types of dermatitis and arthritis; long-term treatment with the oil is advocated for eczema. The fruit has also been used as an aphrodisiac and to stimulate menstrual flow.
- Amazonian natives use it to treat gout, and the Mayan people believed it keeps joints and muscles in top condition, avoiding arthritis and rheumatism.

**Scientific Evidence for Common/Studied Uses:**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Evidence Grade</th>
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<tr>
<td>Hypercholesterolemia</td>
<td>B</td>
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<tr>
<td>Osteoarthritis (knee and hip)</td>
<td>B</td>
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<tr>
<td>Psoriasis</td>
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- **Combination products:** 300 or 600mg of the combination product ASU was given in a clinical trial for treatment of knee osteoarthritis (14). Also, 300mg/kg of ASU has been used up to three months (15) and six months (11) for hip and knee osteoarthritis. Doses of 300mg/kg for two years have also been studied for hip osteoarthritis (16).

**Constituents:** The applicable parts of avocado are the fruit, leaves, and seed. Avocado contains protein, fiber, manganese, phosphorus, iron, potassium, vitamin E, vitamin C, beta-carotene, thiamin, riboflavin, nicotinic acid, and folate.

**Fatty oil:** *chief fatty acids* oleic acid, palmitic acid, linoleic acid, palmitoleic acid (tocopherols, vitamin E), beta sitosterol, persin and persinone A

**Pharmacology:**
The projected mechanism of action is inhibition of superoxide generation from leukocytes. The antioxidant activity on mouse skin may also be due to inhibition of cyclooxygenase-2 (COX-2) by persenone A.
Persenone A inhibited nitric oxide synthase (iNOS) and COX-2 protein expression in mouse macrophage cell line COX-2, iNOS, and NO are involved in biochemical processes responsible for inflammatory diseases.

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**Diagram:**

- PERSIN
- PERSENON A
Anti-inflammatory effects: Avocado/soybean unsaponifiables (ASU) have been shown to reduce cytokines, prostaglandin E2 and metalloproteinase production by human chondrocytes. This finding suggests a potential role for ASU in reducing the harmful effects of IL-1beta in cartilage (47-48). There is also evidence that ASU can increase aggrecan synthesis and reduce catabolic and proinflammatory mediator production by chondrocytes. These results suggest that ASU could have structure-modifying effects in osteoarthritis by inhibiting cartilage degradation and promoting cartilage repair (48). ASU has also been shown to reverse the effect of IL-1beta on gingival fibroblasts for metalloproteinases. This suggests a potential role for ASU in preventing the harmful effect of IL-1beta during periodontal disease (54).

Chondroprotective effects: An experimental in vivo model for studying cartilage destruction was used to study the possible chondroprotective effect of the unsaponifiable constituents of avocado, soya and their combination at a ratio of 1:2. ASU and avocado alone caused significant chondroprotective effects compared to controls in an in vivo model of cartilage destruction. Possible mechanisms of action for this effect include the presence of free radical scavengers, tocopherol and beta-sitosterol, in ASU. Free radical damage is likely involved in cartilage degradation. ASU may also inhibit interleukin-1 (IL-1), which causes cartilage breakdown. IL-1 is released from mononuclear cells, and avocado and ASU have both caused inhibition of mononuclear influx into the granulomatous tissue around cartilage (55).

Cultured bovine articular chondrocytes were treated with various concentrations of ASU, in order to establish the mechanism of action of ASU on articular chondrocytes that may account for the beneficial effects on cartilage metabolism. ASU stimulated the production of transforming growth factors beta-1 (TGF beta-1), TGF beta-2, and plasminogen activator inhibitor 1 (PAI-1). These elements may be involved in the prevention of cartilage degradation and promotion of matrix synthesis required in the repair of articular cartilage. The increased production of matrix metalloproteases, including collagenase and stromelysin by chondrocytes stimulated by interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-alpha), are thought to be responsible for the erosion of cartilage that occurs in osteoarthritis (56).

Lysyl oxidase inhibitory effects: Compound C, isolated from avocado seed oil, inhibited lysyl oxidase activity in vivo and in vitro. Its activity is increased in the presence of tissue remodeling, as in burn scars, wound healing, hepatic fibrosis, granulomas, and lung fibrosis. The lysyl oxidase inhibitory activity of avocado seed oil may explain its use in the treatment of connective tissue disorders (45).

The active constituent in avocado oil is belived, through its ability to inhibit lysyl oxidase activity, to decrease collagen cross-linking, resulting in an increased rate of collagen degradation in vivo. The active constituent responsible for this activity is found in the lipid fraction in the seed oil and unsaponifiable fractions of avocado oil. Theoretically, this effect may play a role in the treatment of certain connective tissue disorders where collagen accumulation is present (56).

Pharmacodynamics/Kinetics:
- Initial response of ASU became statistically superior to placebo treatment after two months of treatment. The effect continued to increase up to six months and lasted for at least two months after treatment was discontinued (11).
**Pre-clinical evidence:** There is some in vitro research that makes ASU appear promising for osteoarthritis. It has been shown that ASU can reduce cytokines, prostaglandin E2 and metalloproteinases production by human chondrocytes. This finding suggests a potential role for ASU ability to inhibit harmful effects of IL-1beta in cartilage (47,48). It has also been shown to increase aggrecan synthesis and reduce catabolic and proinflammatory mediator production by chondrocytes. These results suggest that ASU could have structure modifying effects in osteoarthritis by inhibiting cartilage degradation and promoting cartilage repair (48).

**Evidence:** A systematic review of ASU studies for osteoarthritis (41) found four randomized, placebo controlled, double-blind trials investigating osteoarthritis in the hip or the knee (16;14;11;15). The author of the review concluded that three of four rigorous clinical trials indicated that ASU is an effective symptomatic treatment for osteoarthritis; however the only long-term trial was largely negative.

A well conducted randomized, placebo controlled, double-blind trial with 163 patients found that ASU 300mg/kg for two years did not have any significant effect on the primary endpoint of joint space width (determined with X-ray) in hip osteoarthritis. After a sub analysis, a significant effect in the most severely affected patients was reported. Similarly none of the secondary endpoints (Lequesne’s algofunctional index score from baseline to month 12, spontaneous pain described by Visual Analag Scale, NSAID intake, patient and physician overall assessment, number of days on sick leave, number of patients requiring hip replacement) were significantly reduced. The authors concluded that even if ASU failed to demonstrate a structural effect in the overall population, ASU did significantly reduce progression of joint space narrowing in the post-hoc analysis of severely affected patients.
Evening Primrose

- Name: Oenothera biennis L. (Onagraceae)
- Part(s) Used: Seed oil
- Evening primrose is a plant native to North America, but it grows in Europe and parts of the Southern hemisphere as well.
- Pharmacopoeial and Other Monographs:
  - BP 2007
  - Martindale 35th edition
  - Ph Eur 2007

Traditional medicine

- Evening primrose oil has been used as a folk or traditional remedy for eczema (a condition in which the skin becomes inflamed, itchy, or scaly because of allergies or other irritation).
- More recent folk uses include:
  - other conditions involving inflammation, such as rheumatoid arthritis;
  - conditions affecting women’s health, such as breast pain associated with the menstrual cycle, menopausal symptoms, and premenstrual syndrome (PMS);
  - Cancer
  - Diabetes.
• An infusion of the whole plant has traditionally been used for asthmatic coughs, and as a sedative painkiller.
• Externally, poultices were reputed to ease bruises and to speed wound-healing.
• Nowadays evening primrose oil is used for premenstrual syndrome, psoriasis, multiple sclerosis, hyperc holesterolaemia, rheumatoid arthritis, Raynaud’s phenomenon, asthma and diabetic neuropathy.

• **Dosage**
  • Atopic eczema: 6–8 g daily (adults); 2–4 g daily (children); cyclical and non-cyclical mastalgia: 3–4 g daily.
  • The manufacturer advised that treatment for three months may be necessary before a clinical response is observed.

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**Constituents**

**Fixed oils** 14%, cis-Linoleic acid (LA) 72% (65–80%), cis-gamma-linolenic acid (gamolenic acid, GLA) 2–16%, oleic acid 9%, palmitic acid 7% and stearic acid (3%).\(^{(3\text{-}7)}\)
Pharmacological Actions

• The actions of evening primrose oil are attributable to the essential fatty acid content of the oil and to the involvement of these compounds in prostaglandin biosynthetic pathways.

• Interest in the seed oil of the evening primrose plant lies in its essential fatty acid content, in particular in the linoleic acid (LA) and gamolenic acid (GLA) content. Both of these compounds are prostaglandin precursors and dietary gamolenic acid supplementation has been shown to increase the ratio of non-inflammatory to inflammatory prostaglandin compounds.

In vitro and animal studies

• Gamolenic acid and its metabolite dihomogamma-linolenic acid (DGLA) are precursors of both the inflammatory prostaglandin E2 (PGE2) series via arachidonic acid (AA), and of the less inflammatory prostaglandin E1 (PGE1) series.

• Actions attributed to PGE1 include anti-inflammatory, immunoregulatory and vasodilatory properties, inhibition of platelet aggregation and cholesterol biosynthesis, hypotension and elevation of cyclic AMP (inhibits phospholipase A2).

• Dietary supplementation with gamolenic acid has been noted to have a favourable effect on the DGLA:AA ratio. Although an increase in arachidonic acid concentrations is also seen, this is much smaller and less consistent compared with the increase seen for DGLA.
• Contributory factors to this negative effect on arachidonic acid are PGE1 and 15-hydroxy-DGLA.
• The latter inhibits conversion of arachidonic acid to inflammatory lipoxigenase metabolites including leukotrienes, whilst PGE1 inhibits the enzyme phospholipase A2 which is required for the mobilisation of arachidonic acid from phospholipid membrane stores.
• Gamolenic acid is not normally obtained directly from dietary sources and the body relies on metabolic conversion from dietary LA.
• This conversion is readily saturable and is considered to be the rate-limiting step in the production of gamolenic acid.
• A reduced rate of LA conversion to gamolenic acid has been observed in a number of clinical situations including ageing, diabetes, cardiovascular disorders and high cholesterol concentrations, high alcohol intake, viral infections, cancer, nutritional deficits, atopic eczema and premenstrual syndrome.
• Direct dietary supplementation with gamolenic acid effectively bypasses this rate-limiting conversion step and has a beneficial effect on the ratio of inflammatory : non-inflammatory prostaglandin compounds.

• Gamolenic acid, administered as evening primrose oil, can prevent or reverse diabetic neuropathy in animal models.
• Administration of gamolenic acid to animals has been reported to prevent or attenuate renal damage.
• Gamolenic acid decreases blood pressure and platelet aggregation in animals.
Clinical studies

• 1-Cyclical/non-cyclical mastalgia and premenstrual syndrome:
  • PGE1 is thought to modulate the action of prolactin. Abnormal concentrations may result in an excessive peripheral action of prolactin.
  • The use of evening primrose oil for the treatment of premenstrual syndrome has been rationalised on the grounds that hypersensitivity to prolactin is due to low levels of PGE1.
  • High levels of linoleic acid and low levels of gamma-linolenic acid have been observed for patients with premenstrual syndrome.
  • Several placebo-controlled studies in the older literature have reported that gamolenic acid is better than placebo in the treatment of premenstrual syndrome and/or breast pain.

• 2-Diabetic neuropathy:
  • Diabetes has been associated with reduced ability to desaturate essential fatty acids, with deficits resulting in abnormal neuronal membrane structure. A double-blind, placebocontrolled trial has described reversal of diabetic neuropathy by gamolenic acid.

• 3-Multiple sclerosis
  • Patients with recent onset or less severe forms of the disease are more likely to respond.
  • It is suggested that linoleic acid is involved in the immunosuppressive effect at the cellular level and may be of use when combined with a low animal fat/high polyunsaturated fat diet.

• 4-Rheumatoid arthritis
  • A randomised, double-blind trial has demonstrated a significant improvement in subjective symptoms of rheumatoid arthritis (RA) (indicated by a reduction in required non-steroidal antinflammatory drug treatment)
• **5-Coronary heart disease**
  • Abnormal intake and metabolism of EFAs (both n-3 and n-6) are thought to be important risk factors for coronary heart disease.
  • gamolenic acid has been reported to decrease blood pressure and platelet aggregation in humans.

• **6-Gastrointestinal disorders** :
  • A double-blind placebo-controlled crossover trial has indicated a beneficial effect of evening primrose oil on irritable bowel syndrome exacerbated by premenstrual syndrome. A beneficial effect superior to that of fish oil or placebo has been reported for evening primrose oil in ulcerative colitis.

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**Side-effects, Toxicity**

• Mild gastrointestinal effects, indigestion, nausea and softening of stools and headache have occasionally occurred.
  • Evening primrose oil should be used with caution by such patients and those with a history of epilepsy and schizophrenic patients being treated with epileptogenic drugs such as phenothiazines
  • Evening primrose oil should not be taken during pregnancy. As LA and gamolenic acid occur naturally in breast milk, it is reasonable to expect that evening primrose oil can be taken during breastfeeding.

• Toxicity studies have indicated evening primrose oil to be nontoxic
Prostaglandin biosynthesis pathway

- Numerous stimuli (e.g., epinephrine, thrombin and bradykinin) activate PLA₂ which hydrolyzes arachidonic acid from cellular membrane phospholipids.
- Both PKC phosphorylation and the Ca²⁺ ions activate the ER membrane-associated cPLA₂ isoforms which, when activated, hydrolyze arachidonic acid from PIP₂.
- Arachidonic acid is converted to PGH₂ via the action of the bi-functional enzymes COX-1 and COX-2.
- Prostaglandins and thromboxanes are synthesized from PGH₂.
Probable mechanism for the cyclooxygenation of arachidonic acid by PGH synthase
Lakoterinehā

- Enzyme 5-lipoxygenase (5-LO) and the 5-LO inhibitors block the 5-LO activating protein (FLAP) and may help in treating atherosclerosis.
- Zileuton (trade name ZYFLO) is an orally active inhibitor of 5-lipoxygenase, and thus inhibits leukotrienes (LTB$_4$, LTD$_4$, LTE$_4$, and LTE$_5$) formation. Zileuton is used for the maintenance treatment of asthma.
- Zileuton is indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.
- Drugs such as MK-886 block the 5-lipoxygenase activating protein (FLAP) and may help in treating atherosclerosis.

Lakoterinehā:
- Lakoterinehā in inflammation and in the treatment of asthma.
- LTBA and LTBC are converted to LTE4, LTD4, and LTE5 by the enzyme 5-lipoxygenase.
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- Drugs such as MK-886 block the 5-lipoxygenase activating protein (FLAP) and may help in treating atherosclerosis.
مکانیسم پیشنهادی لیپو اکسیژناسیون آراشیدونیک اسید به هیدروکسی ایکوزاتترانوئیدها (HETEs)

There are several lipoxygenases that act upon different positions on the arachidonic acid, mainly 5, 12 and 15, although an 8-lipoxygenase is also relevant, to produce various hydroxyeicosatetraenoic acids (HETEs) and then into leukotrienes and lipoxins (LXs).

ترومبوکسان‌ها

ترومبوکسان A2 یک عامل ایجاد لخته (ترومبوژنیک) و انقباض عروق است که تولید می‌گردد و در ماکروفاژها و ریه نیز تولید می‌گردد. آسپرین در رقابت با آراشیدونیک اسید روی جایگاه فعال آنزیم PGH synthase که در ضمن با استیله نمودن گروه هیدروکسی اسید سرین در جایگاه فعال آنزیم سیکلواکسیژناز نیز منجر به مهار غیر قابل برگشت آن می‌گردد. بنابراین 70 میلیگرم آسپرین می‌تواند 95% آنزیم پلاکت و فعالیت سیکلواکسیژناز را غیرفعال کند که در نتیجه آن ترومبوکسان A2 تولید نمی‌شود. در مقابل بیوسنتز PG12 که مهارکننده دیگر انعقاد پلاکتی است تحت تأثیر آسپرین قرار نمی‌گیرد زیرا سلول‌های اندوتیال سریعاً بیوسنتز PGH synthase جدید تولید می‌کنند. بنابراین آسپرین هبلاک پلکتی و فعالیت سیکلواکسیژناز را پایان داده ولی در مقابله با اثر ضد انعقاد PG12 مقایسه با دیگر داروهای NSAID می‌تواند نمی‌گردد.
Polyunsaturated fatty acids (PUFAs) competition with 20:4

• When omega-3 and omega-6 fatty acids are consumed they are incorporated into cell membranes in all tissues of the body.
• Because of this fact, dietary changes in the composition of PUFAs can have profound effects on a cell's function because the membrane lipids serve as a source of precursors for the synthesis of important signaling molecules involved in cell growth and development as well as modulation of inflammation.
• omega-3 and omega-6 PUFAs compete for incorporation into cell membranes
• omega-3 PUFAs compete with the enzymes that convert arachidonic acid into the pro-inflammatory eicosanoids (PGE\(_2\), TXA\(_2\), and LTB\(_4\)).
• The net effect of increasing dietary consumption of omega-3 PUFAs, relative to omega-6 PUFAs, is to decrease the potential for monocytes, neutrophils, and eosinophils (i.e. white blood cells called leukocytes) to synthesize potent mediators of inflammation and to reduce the ability of platelets to release TXA\(_2\), a potent stimulator of the blood coagulation cascade.

Mixodine

• Food supplement made of turmeric, Ginger and pepper extracts concentrated in Curcumin, Piperine and Gingerol

• TURMERIC AND GINGER EXTRACTS POTENTIALIZED BY PIPERINE
• HELPS TO DECREASE JOINT INFLAMMATION
• HELPS TO MAINTAIN CELL BALANCE
• DECREASES POLLUTANTS ATTACKS ON CELLS

• Composition:
  Curcumin: 300mg
  Gingerol: 7.5mg
  Piperine: 3.75mg
• **Curcumine (turmeric concentrate):**

  * curcumin binds to and inhibits lipoxygenase enzymes
  * Preventing the formation of molecules like eicosenoids, which promote cell disbalances.

  * Curcumin inhibits APN, amino peptidase N
  * Tumor cells produce unusually high levels of APN which helps them to invade healthy tissue. Curcumin prevents APN, anti-cancer effect.

  * suppress the activity of NF-kappa ?, a cancer promoting protein

• **Curcumin, a component of turmeric, has been shown to be non-toxic, to have antioxidant activity, and to inhibit such mediators of inflammation as NFkappaB, cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS).**

• **Gingerol(Ginger)**

  * Excellent inhibition of the production of PGE2 and nitric oxide, effective in inflammation
  * Inhibition of TNF-a
  * suppress the activity of NF-kappa B, a cancer-promoting protein
  * inhibits cyclooxygenase-II (COX-II)

• **Black pepper (piperin)**

  Piperine inhibits the conversion of curcumin metabolites which are eliminated, thus increasing the passage of curcumin in plasma so it enhances curcumin bioavailability.
Curcuma longa

- Turmeric is used traditionally in the Chinese and Ayurvedic systems of medicine, particularly as an anti-inflammatory and for the treatment of flatulence, jaundice, menstrual difficulties, hematuria, hemorrhage, and colic.
- *Curcuma longa (turmeric) has a long history of use in Ayurvedic medicine as a treatment for inflammatory conditions.*
- Turmeric can also be applied topically in poultices to relieve pain and inflammation.

Active Constituents:

- The active constituents of turmeric are the curcumin and various volatile oils, including tumerone, atlantone, and zingiberon
ANTIOXIDANT PROPERTIES OF CURCUMIN

- The anti-inflammatory effect of curcumin is most likely mediated through its ability to inhibit cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS).
- Improper upregulation of COX-2 and/or iNOS has been associated with the pathophysiology of certain types of human cancer as well as inflammatory disorders.
- Nitric oxide (NO) has an unpaired electron and is therefore a free-radical species.
- It is a short-lived, lipophilic molecule generated from l-arginine by NO synthase (NOS).
- NO is involved physiologically in vasorelaxation, neurotransmission, inhibition of platelet aggregation, immune defense, and intracellular signaling. However, NO reacts with O₂ to form peroxynitrite (ONOO⁻), which is a powerful oxidant.
- It is now beyond doubt that oxidants are generated in vivo and can cause significant damage to cells.
- This oxidative stress in cells results in severe metabolic dysfunctions, including loss of cell integrity, enzyme function, genomic stability, and so forth, which ultimately lead to pathogenesis of many human diseases (e.g., inflammation).

- Curcumin is known to protect biomembranes against peroxidative damage
- Curcumin is an unique antioxidant, which contains a variety of functional groups, including the B-diketo group, carbon–carbon double bonds, and phenyl rings containing varying amounts of hydroxyl and methoxy substituents.
- curcumin can degrade into ferulic acid, and vanillin at basic pH within 30 min which are well-established antioxidants.
ANTI-INFLAMMATORY PROPERTY OF CURCUMIN

1-Effect of Curcumin on Cyclooxygenases and Lipoxygenases:

- The anti-inflammatory properties of curcumin have been attributed, at least in part, to suppression of prostaglandins (PGs) synthesis.
- Cyclooxygenase (COX) is a key enzyme responsible for the conversion of arachidonic acid to PGs.
- There is growing evidence that inhibitors of COX-2 activity are useful for treating inflammation and preventing or treating cancer.
- An expanding body of evidence suggests that curcumin inhibits the expression of COX-2.
- Dietary curcumin significantly inhibits phospholipase A2 in colonic mucosa and tumors, leading to the release of arachidonic acid from phospholipids, alters COX and LOX activities, and modifies PGE2 levels.
- Therefore, curcumin would appear to be a safe, natural COX-2 inhibitor in humans, given its safety profiles and demonstrated anti-inflammatory activity.

2-Effect of Curcumin on Inducible Nitric Oxide Synthase

- Another enzyme that plays a pivotal role in mediating inflammation is inducible nitric oxide synthase (iNOS).
- iNOS catalyzes the oxidative deamination of L-arginine to produce NO, a potent pro-inflammatory mediator.
- iNOS has been shown to be involved in the regulation of COX-2 and, hence, the subsequent production of pro-inflammatory PGs.
- In addition to COX-2, iNOS also appears to be a target for the anti-inflammatory effect of curcumin. Curcumin is reported to inhibit the NO production and expression of iNOS protein.
• **3-Efffect of Curcumin on Nuclear Factor-κB**
  
  One of factors that regulate expression of genes involved in controlling inflammatory responses, cell adhesion, and so forth is nuclear factor-κB (NF-κB).
  
  It has been found that oxidative stress activates NF-κB DNA-binding activity. Because curcumin has been known as an antioxidant, its inhibitory effects on oxidative stress might be mediated through the suppression of NF-κB DNA-binding activity.
  
  It has been reported that curcumin inhibited IKB kinase (IKK), suppressed both constitutive and inducible NF-κB activation and potentiated tumor necrosis factor (TNF)-induced apoptosis.
  
  The IKB kinase (IKK) is an enzyme complex that is involved in propagating the cellular response to inflammation.
  
  Inhibition of IκB kinase (IKK) and IκK-related kinases, IKBKε (IKKe) and TANK-binding kinase 1 (TBK1), has been investigated as a therapeutic option for the treatment of inflammatory diseases and cancer. The small-molecule inhibitor of IKK-β SAR113945, developed by Sanofi-Aventis, was evaluated in patients with knee osteoarthritis.

• **Summary**

  Curcumin, with its impressive antioxidant and anti-inflammatory properties, was found to be a genuine natural product in treating a wide array of diseases. Its antioxidant property is believed to be due to the presence of different functional groups, including methoxy, phenoxy, and carbon–carbon double bonds in its structure.
  
  Its remarkable anti-inflammatory property kept it in the lime light over the decades in treating inflammatory-mediated diseases including cancer, atherosclerosis, diabetes, rheumatoid arthritis, and so forth.
  
  Its anti-inflammatory property appears to be mediated through the inhibition of induction of COX-2, LOX, and iNOS and the production of cytokines such as interferon-γ, tumor necrosis factor, and many other transcription factors such as NF-κB.
  
  IFNγ is an important activator of macrophages and inducer of Class I major histocompatibility complex (MHC) molecule expression. Aberrant IFNγ expression is associated with a number of autoimmune and autoinflammatory diseases.
Boswellia serrata

- Boswellia serrata (frankincense) is a moderate-to-large branching tree (growing to a height of 12 feet) found in India, North-eastern Africa, and the Middle East.
- Strips of Boswellia bark are peeled away, yielding a gummy oleo-resin. Extracts of this gummy exudate have been traditionally used in the Ayurvedic system of medicine as an anti-arthritic, astringent, stimulant, expectorant, and antiseptic.
- Ayurveda describe the antirheumatic (antiarthritis) activity of gugguls—the gum-resins of trees.
- This gummy resin is also mentioned in traditional Ayurvedic and Unani texts as an effective remedy for fevers (antipyretic), bronchitis, asthma, cough.

Active Constituents

- Up to 16 percent of the resin is essential oil, the majority being alpha-thujene and p-cymene.
- Four pentacyclic triterpene acids are also present, with beta-boswellic acid being the major constituent.
Mechanisms of Action

• Animal studies performed in India show ingestion of a defatted alcoholic extract of Boswellia decreased polymorphonuclear leukocyte infiltration and migration, decreased primary antibody synthesis, and almost totally inhibited the classical complement pathway.

• In vitro testing reveals boswellic acids, isolated from the gum resin of Boswellia, in a dose-dependent manner block the synthesis of proinflammatory 5-lipoxygenase products, including 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B4 (LTB4), which cause bronchoconstriction, chemotaxis, and increased vascular permeability.

• Boswellia inhibits human leukocyte elastase (HLE), which may be involved in the pathogenesis of emphysema. HLE also stimulates mucus secretion and thus may play a role in cystic fibrosis, chronic bronchitis, and acute respiratory distress syndrome.

• Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause a disruption of glycosaminoglycan synthesis, accelerating articular damage in arthritic conditions.

• An in vivo animal study examined Boswellia extract and ketoprofen for effects on glycosaminoglycan metabolism. Boswellia significantly reduced the degradation of glycosaminoglycans compared to controls; whereas, ketoprofen caused a decrease in total tissue glycosaminoglycan content.
Clinical Indications

• **Inflammatory Bowel Disease**
  • An animal study was conducted to determine the efficacy of Boswellia extract and acetyl-11-keto-β-boswellic acid (AKBA), on leukocyte-endothelial cell interactions in inflammatory bowel disease
  • It was observed that Boswellia extract and AKBA decreased rolling (up to 90%) and adherent leukocytes (up to 98%), attenuated tissue injury scores, and significantly reduced macroscopic and microscopic inflammation of the gut mucos

• **Ulcerative Colitis**
  • A follow-up study of chronic colitis patients taking gum resin of Boswellia (900 mg daily in three divided doses for six weeks) and sulfasalazine (3 g daily in three divided doses for six weeks) again showed similar improvements.

• **Asthma**
  • In a 1998 study of Boswellia’s effects on bronchial asthma, 40 patients took 300 mg of a Boswellia preparation three times daily for six weeks, while an other 40 patients took a placebo. Seventy percent of patients taking Boswellia demonstrated significant disease improvement, measured by symptomatology and objective measures of lung and immune function.
• **Arthritis**

  In a double-blind, placebo-controlled trial, Boswellia demonstrated beneficial effect on knee osteoarthritis. Thirty patients were given either 1,000 mg Boswellia daily or placebo in three divided doses for eight weeks. Patients in the Boswellia group experienced a significant decrease in pain and swelling and increase in range of motion compared to placebo.

• **Dosage**

  For inflammatory or asthmatic conditions, 300-400 mg of a standardized extract (containing 60% boswellic acids) three times daily is suggested.