Angina pectoris

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I. Definition

Angina pectoris (AP) represents a clinical syndrome that occurs when myocardial oxygen demand exceeds supply.[1]

Angina pectoris has a wide range of clinical manifestations.

Symptoms may also include shortness of breath, nausea, and sweating.

Symptoms result from insufficient oxygen supply to myocardial tissue.

No definitive diagnostic tool covers all patients with angina. This, combined with its variable clinical presentation, makes angina a particular clinical challenge for emergency physicians

Angina is a symptom of coronary artery disease caused by blockage of a coronary artery

II. Types [2]

Angina includes variant types. The type depends on the cause and whether rest or medication relieves symptoms.

- **Stable angina**:-Stable angina is the most common form of angina. It usually occurs during activity (during exercise) and resolves with rest or angina drugs. For example, pain that occurs when walking uphill or in cold weather may be angina.

  Pain in stable angina is predictable and usually resembles previous episodes of chest pain. Chest pain usually lasts for a short time, perhaps he no more than 5 minutes.

- **Unstable angina** (emergency care):- Unstable angina is unpredictable and occurs at rest. Or, it occurs when angina pain worsens and physical activity decreases. It is typically severe and lasts longer than stable angina, perhaps 20 minutes or more. The pain does not go away with rest or the usual angina drugs. If blood flow is not improved, the heart will starve of oxygen and a heart attack will occur.

  Unstable angina is hazardous and needs immediate medical attention.
- **Angina pectoris variant** (Prinzmetal angina):- Atypical angina, also known as Prinzmetal angina, is not due to coronary artery disease. It is caused by a spasm in an artery of the heart, which temporarily reduces blood flow. The primary symptom of variant angina is severe chest discomfort. It most commonly occurs during the resting-night cycle. Medicines for angina pectoris can relieve pain.

- **Recalcitrant angina:-**Despite a mix of drugs and lifestyle modificatios, angina attacks are frequent

III. Causes [2]

Reduced blood supply to the heart muscle is what causes angina. The oxygen that the heart muscle requires to survive is carried by blood.

Ischemia is the medical term for the illness brought on by inadequate oxygen delivery to the heart muscle. The most common cause of reduced blood flow to the heart muscle is coronary artery disease (CAD).

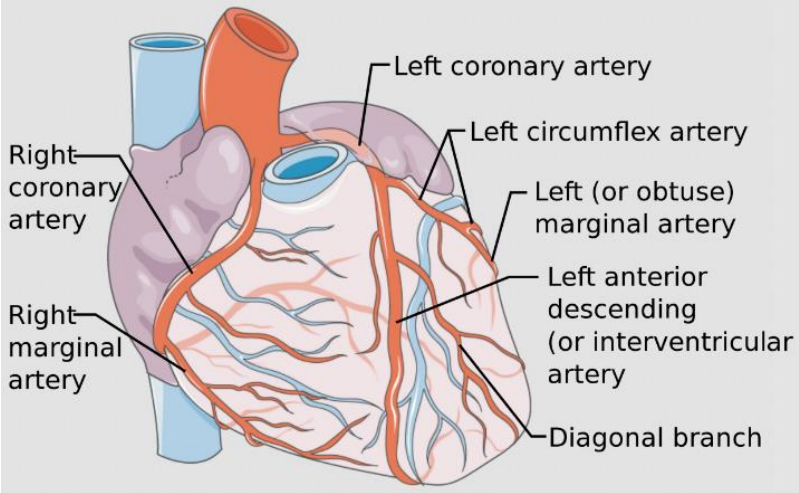
The heart's (coronary) arteries might narrow due to the fatty deposits known as plaques.The medical word for this is atherosclerosis.

A blood clot or plaque rupture in a blood vessel can abruptly restrict or stop blood flow through a constricted artery.

The heart muscle may be able to function on the lower amount of blood flow when there is little oxygen demand, such as while one is at rest, without experiencing angina symptoms. However, angina can occur when the body requires more oxygen, as it does during exertion.

IV. Pathophysiology

Our general understanding of the pathophysiology of myocardial ischemic syndrome has expanded significantly over the past two decades. The main dysfunction of angina pectoris is the decreased oxygen supply to the heart muscle cells. Her two main mechanisms by which delivery is affected appear to be coronary artery stenosis and endothelial dysfunction. Other mechanisms that affect oxygen delivery can also cause symptoms.



- **Extracardiac causes of angina pectoris include**

anemia, hypoxia, hypotension, bradycardia, carbon monoxide exposure, and inflammatory disease. The end result is a shift towards anaerobic

metabolism in cardiomyocytes. This is followed by stimulation of the pain receptors that innervate the heart. These pain receptors are ultimately directed to afferent pathways carried by multiple nerve roots from C7 to T4.Referred pain in angina is thought to occur because these afferent pathways also carry pain fibers from other areas (arms, neck, shoulders, etc.)[3]

- **Coronary Artery Stenosis**

  In the majority of instances, it appears that coronary artery narrowing is the cause of myocardial ischemia.

  When atherosclerotic disease reduces or stops blood flow via the coronary artery circulation, interfering with normal laminar blood flow, this has clinical importance even a slight alteration in blood vessel's width can have significant consequences This result is predicted by the Poiseuille law:-

  every change in lumen radius causes an exponential drop in flow rate.

  Even slight changes in diameter have a significant impact on flow rates, similar to a narrower paediatric airway.

  As a result, when a lumen is reduced by a fifth, the flow rate is reduced by roughly half. This suggests that even a slight alteration in the size of a plaque in a coronary artery can have an impact on the oxygenation of the area surrounding that vessel.

  An increase in demand has the potential to cause the epicardial vessel, where atherosclerosis frequently occurs, to enlarge via autoregulatory processes. Angina develops when this compensatory mechanism is overloaded, either by major increases in cardiac demand or by massive plaques (usually regarded as 70% or greater occlusion).[4]

- **Endothelial Factor**

  Endothelial factor also plays an important role in angina. During sympathetic stimulation, the endothelium is exposed to both vasoconstrictor and vasodilatory mediators. Although α-agonists (catecholamines) directly cause vasoconstriction, endothelial nitrous oxide synthase produces nitrous oxide (NO) to counteract this contractile force by vasodilation.

  NO production is reduced or absent in diseased coronary arteries. In such situations, the catecholamine drive may overwhelm the autoregulatory mechanisms. In addition, the endothelium of the plaque-laden artery itself can become dysfunctional. This limits the ability of arterial endothelium to generate mediators that protect healthy arteries from further vasoconstriction, support dilation, and protect against platelet aggregation. Small lesions in these vessels can produce incompletely occluded platelet aggregates[(4)]. This further impedes flow through the affected vessel.

  In diseased hearts, these two factors, coronary stenosis and endothelial dysfunction, synergistically reduce oxygen supply to the myocardium. The net result is angina.

- **External Factors**

  External factors can also play a role under certain circumstances. The oxygen-carrying capacity of blood depends on many factors. The most important of these is the amount of hemoglobin. Changes in the blood's ability to carry oxygen can cause angina pectoris. Any degree of anemia can cause symptoms of angina. In an increased demand scenario.

Climbing stairs, being stressed, or having sexual intercourse, angina symptoms may occur.(5)

Abnormal hemoglobins such as methemoglobin, carboxyhemoglobin, or various hemoglobinopathies create an environment that increases the risk of developing angina.

Other external factors affecting hemoglobin formation, such as lead poisoning and iron deficiency, lead to similar reductions in oxygen transport capacity. Mechanisms that interfere with the oxygen supply to red blood cells have similar effects. Therefore, pulmonary causes such as pulmonary embolism, pulmonary fibrosis or scarring, pneumonia, or congestive heart failure can exacerbate angina. Hypoxic environments such as B. Traveling to higher altitudes has similar consequences due to lower atmospheric oxygen concentrations.

- **Variant angina**

Variant angina's cause is still poorly known. According to research, inflammatory mediators may cause localised vasospasm in the coronary arteries. Another explanation is that microvascular circulation reduces perfusion.Transient hypoperfusion and oxygen deprivation may occur in this tiny lumen as a result of spasm or periodic narrowing.(6)

V. Physical Examination

A physical examination may show signs of an adrenergic state. Tachycardia, tachypnea, hypertension and/or sweating can be observed. In addition, subsequent pulmonary edema or ischemia due to loss of contractility with decreased S1 intensity can lead to the appearance of crackling sounds. (7)

As in many emergency departments, a physical examination for angina can serve as a marker of response to treatment. Important complications identifiable on physical examination are aortic stenosis, gastrointestinal bleeding, and airway obstruction. Unfortunately, there are no laboratory findings characteristic of angina. In addition, there were no physical examination findings to rule out disease status.

Of note, reproducibility of chest wall pain on palpation may reduce the likelihood of angina, but this alone does not rule out angina or myocardial infarction.[8,9]

VI. Laboratory Investigations

Electrocardiography

chest x-ray.

Cardiac biomarkers (such as troponin)

VII. Risk Factors

Factors that increase the risk of Angina	Factors that decrease the risk of Angina
1.Cigarette smoking 2.Raised serum cholesterol 3.Hypertension, Diabetes 4. Increased personal stress 5.Abdominal obesity	1.Regular consumption of fresh fruit and vegetables 2.Regular exercise 3.Moderate alcohol consumption 4.Modification of factors that increase the risk of Angina

VIII. Treatment

i. Pharmacological Treatment

ii. Surgical treatment:

iii. Herbal treatment:

If medical Treatment failure:

1. Coronary Angioplasty (or Balloon Dilation)
2. Coronary Artery Bypass Graft
3. Atherectomy
4. Stent Placement

i. Pharmacological Treatment[2]

a. Specific Drug Therapies

1. Organic Nitrates
2. Ca++ Channel Blockers
3. Beta blockers
4. New drugs such as ranolazine

b. General treatment

1- Mental and physical rest

2- Sedatives

3- Analgesics

4- Dietary fat reduction

5- Antihyperlipidemic drugs

6- Platelet aggregation inhibitors

7- All Modification of predispositions (smoking, hypertension, D.M., obesity).

iii. Herbal treatment

Aim of treatment:

1- Increased coronary blood flow, decreased oxygen demand, or both

2- For atypical angina Prophylaxis of coronary spasm

3- For unstable angina Tendency to modified intracoronary thrombosis (with heparin and aspirin).

Herbs that may help with angina include:

1. **Hawthorn** الزعرور

There are 280 known species of hawthorn,

Family:-Rosaceae.

It is a commonly used herb for minimizing and relief cardiovascular diseases.

Active constituents **(10,12-18)**

Flavonoids and OPCs are the two main classes of bioactive components found in hawthorn fruits, leaves, and flowers, respectively.

- flavonoids (0.1%-1%)in fruits, (1%-2% in leaves and flowers)
- oligomeric proanthocyanidins (OPCs, 1%-3% in fruits or leaves with flowers)
- triterpene acids (0.5%-1.4% in fruits)
- organic acids (2%-6%)
- sterols
- trace amounts of cardioactive amines.

pharmacological action

Mechanism

i. **Improving blood circulation, and removing blood stasis by**

enhancing blood flow and eliminating blood clots by increasing cardiac output and coronary blood flow while decreasing oxygen consumption(19-23)

These activities might be connected to the inhibitory effect on phosphodiesterase.(23,24)

The herb is used to treat various heart problems, like heart failure, angina pectoris, hypertension with myocardial insufficiency, cardiac rhythm, and atherosclerosis.[11]

ii. **Antiarrhythmic Activity due** aconitine, calcium chloride, and chloroform-adrenaline . [25-27]

iii. **Hypotensive Activity** due flavonoid, OPC, and triterpene acid extracts

iv. **Hypolipidemic Activity** decrease the serum levels of cholesterol, LDL-cholesterol, and triglyceride in hypercholesterolemic and atherosclerotic animals. It also suppresses deposition of fat in the liver and aorta. [28-31]

CLINICAL STUDIES

Hawthorn preparations may be helpful for angina, mild arrhythmia, hypertension, and congestive heart failure in its early stages.

This has been demonstrated in many clinical studies[30,32-40]as it decrease heart rate, improving exercise tolerance and pressure/heart rate product, and lowering serum lipids in people with hyperlipidemia or stage II heart failure according to the NYHA. However, there was no impact on diastolic blood pressure in some of these investigations.[34,35]

Although serum lipids in the patients with hyperlipidemia were reduced by hawthorn in one clinical trial,[30] the study was not controlled. Thus, the clinical benefit of this effect requires further confirmation.

Side effects, toxicity, and drug interactions

No significant Toxicity or side event have been observed in clinical trials.

digitalis, beta-blockers, and other hypotensive drugs was potentiated there effect with this plant .Recalculate of the drug dosage may be necessary.[41,42]

2. **Ammi Visnaga** الخلة البلدية

Ammi species belong to the Apiaceae family and contain bioactive compounds (mainly coumarins and flavonoids) with important biological activities.

Active ingredients[43-48]

Comes with Ami Visnaga

- γ-pyrone (up to 4% furanochromones),
- khellin (0.3-1.2%), Kerinol, Kelor, Kerinine
- Visnagin (0.05-0.30%),
- Contains fatty oils (up to 18%)
- Coumarin (0.2-0.5%),
- Most importantly pyranocoumarin visnadine (0.3%)

Pharmacological actions

Traditional uses:

Fruit of Ammi visnaga used to treat mild angina symptoms, also asthma, bronchial asthma or Postoperative treatment of spastic bronchitis and conditions associated with the presence of uroliths.[49]

cardiovascular effects

Ammi visnaga induced relaxation of smooth muscle, including ureter and coronary arteries[50]

Intravenous administration of visnagin lowered blood pressure without significant changes in heart rate[51-53]

Samidin and khellol glucoside induced positive inotropic effects on the heart[54]

Clinical studies

Thirty-eight cases of angina pectoris and eight cases of coronary thrombosis were studied by Kellin. Successive treatment by the oral or intramuscular route, or both, produced favorable results in 35 of 38 patients with angina.

Continued administration of khellol for several weeks in her eight patients after coronary thrombosis appeared to be successful[54].

Contraindications and side effects

- Exposure to sunlight and other UV light sources should be avoided during treatment with Ammi visnaga and its ingredients. due to light sensitivity

- Long-term use or overdose of the drug can cause nausea, dizziness, loss of appetite, headaches, trouble sleeping, and very strong side effects.
- Higher doses (equivalent to ≥100 mg khellol) caused reversible increases in liver enzyme levels[55,56]

3. **Ginkgo Biloba**

الجنكة بيلوبا أو شجرة المعبد

The ginkgo biloba officially known as The maidenhair tree and more commonly known as just the ginkgo, is one of the most distinctive trees.

Family :- Ginkgoaceae

Active ingredient[57,58]

Primary active constituents in the leaves of *G. biloba* are

- flavonoid glycosides 24%
- ginkgolides (types of diterpines which are potent inhibitors of platelet-activating factor).(50)
- terpene lactones 6%

pharmaceutical result

Numerous pharmacological activities of G. biloba leaf extract include antioxidant and cardioprotective actions.

According to Mahadevan and Park, the leaf extracts' cardioprotective effects come from their antioxidant and antiplatelet properties as well as their ability to improve blood flow by releasing nitric oxide and prostaglandins.[59]

4. **Squill [60] البصل**

Species (Family)

Drimia maritima (L.) Stearn (Asparagaceae)

Synonyms

Scilla, Sea Onion, Urginea, Urginea maritima (L.) Baker, Urginea scilla Steinh., White Squill.

Parts Used

Bulb (red and white varieties)

Active Constituents

1. Cardiac glycosides:
    - Scillaren A and proscillaridin A (major constituents).
    - others include: glucoscillaren A, scillaridin A, scillicyanoside, scilliglaucoside, scilliphaeoside, scillicoeloside, scillazuroside and scillicryptoside.
    - Scillaren B represents a mixture of the squill glycosides.

2. Flavonoids:

   Apigenin, dihydroquercetin, isovitexin, iso-orientin, luteolin, orientin, quercetin, taxifolin and vitexin.
3. Stigmasterol.
4. Tannin.
5. Volatile oils.
6. fixed oils.

Food Use

Squill has been prohibited as a food flavouring according to "The Food Additives and Contaminants Committee" recommendations.

Herbal Use

- Squill has expectorant, cardioactive, cathartic, and diuretic, emetic, properties.
- Traditionally:

it has been used for chronic bronchitis, asthma with bronchitis, whooping cough, and specifically for chronic bronchitis with scanty sputum.

Pharmacological Actions

1. **Cardiac actions**
    - The aglycone components of the cardiac glycoside constituents possess digitalis-like cardiotonic properties. However, the squill aglycones are poorly absorbed from the gastrointestinal tract and are less potent than digitalis cardiac glycosides.
    - Squill extracts have been reported to exhibit peripheral vasodilatation and bradycardia in anaesthetised rabbits.

2. **Expectorant and emetic action**
    - It has been documented that white squill has expectorant, emetic and diuretic properties.
    - Squill is reported to induce vomiting by both a central action and local gastric irritation. Subemetic or near-emetic doses of squill

appear to exhibit an expectorant effect, causing an increase in the flow of gastric secretions.

3. **Antiseborrhoeic action**

Antiseborrhoeic properties have been documented for methanol extracts of red squill which have been employed as hair tonics for the treatment of chronic seborrhoea and dandruff.

Side-effects, Toxicity

Clinical data

Excessive use of squill is potentially toxic because of the cardiotonic constituents. However, squill is also a gastric irritant and large doses will stimulate a vomiting reflex.

Preclinical data

Red squill is toxic to rats and is mainly used as a rodenticide, causing death by a centrally induced convulsant action. A squill soft mass (crude extract) has been stated to be toxic in guinea-pigs at a dose of 270 mg/kg body weight. A fatal dose for Indian squill (Urginea indica Kunth.) is documented as 36 mg/kg.

Contra-indications, Warnings

Squill may cause gastric irritation and should be avoided by individuals with a cardiac disorder. In view of the cardiotonic constituents, precautions applied to digoxin therapy should be considered for squill.

Drug interactions None documented. However, the potential for preparations of squill to interact with other medicines administered concurrently, particularly those with similar or opposing effects, should be considered. Squill contains cardiac glycosides, and interactions listed for digoxin should be considered for squill.

Pregnancy and lactation

Squill is reputed to be an abortifacient and to affect the menstrual cycle. In addition, cardioactive and gastrointestinal irritant properties have been documented.The use of squill during pregnancy and lactation should be avoided.

5. **Garlic** [61] **الثوم**

Species (Family)

Allium sativum L. (Alliaceae/Liliaceae)

Synonyms

Ajo, Allium

Part Used

Bulb (clove)

Active Constituents

This material is compiled from several sources including

1. **Enzymes**

   Allinase, peroxidases, myrosinase and others (e.g.catalases, superoxide dismutases, arginases, lipases).

2. **Volatile oils** 0.1–0.36%.
   a. Sulfur-containing compounds including alliin, compounds produced enzymatically from alliin including allicin (diallyl thiosulfinate), allylpropyl disulfide, diallyl disulfide, diallyl trisulfide;
   b. ajoene and vinyldithiines (secondary products of alliin produced non-enzymatically from allicin);
   c. Sallylmercaptocysteine (ASSC)
   d. S-methylmercaptocysteine (MSSC)
   e. terpenes include citral, geraniol, linalool, a- and b-phellandrene.

3. **Other constituents**

   Proteins (e.g. glutamyl peptides), amino acids (e.g. arginine, glutamic acid, asparagic acid, methionine, threonine), minerals, vitamins, trace elements, lipids, prostaglandins (A2, D2, E2, F1a, F2).

   Allicin and other sulfur-containing compounds are formed from alliin by the enzyme alliinase when garlic is crushed or chopped. (Alliin and alliinase are separated while the cells of a garlic bulb are intact, but crushing and chopping damage the cells of the bulb, allowing alliin and alliinase to come into contact with each other).

Commercial garlic preparations are often standardised on content of sulfur-containing constituents, particularly to alliin, or on allicin yield. Garlic powder contains not less than 0.45% allicin calculated with reference to the dried drug.

Therapeutic effects

1. Anti-atherosclerotic and cholesterol- and lipid- lowering effects.
2. Antithrombotic and fibrinolytic effects.
3. Antihypertensive effects.
4. Anticancer effects.
5. Antimicrobial effects.

Side-effects, Toxicity

Clinical data

Garlic is generally considered to be non-toxic.

Adverse effects that have been documented in humans include

1. Burning sensation in the mouth and gastrointestinal tract.
2. Nausea.
3. Diarrhea.
4. Vomiting.
5. 'garlic breath' (is one of the most common adverse events were reported).
6. The allergenic potential of garlic is well recognised, and allergens have been identified as diallyl disulfide, allylpropyl sulfide and allicin (the latter may be an irritant).

Contra-indications, Warnings

In view of the pharmacological actions documented for garlic, there may be an increased risk of bleeding with use of garlic supplements in patients undergoing surgery. Gastrointestinal irritation may occur particularly if the clove is eaten raw by individuals not accustomed to ingesting garlic.

Drug interactions

In view of the documented pharmacological actions of garlic, the potential for preparations of garlic to interfere with other medicines administered concurrently, particularly those with similar (such as antiplatelet and anticoagulant agents) or opposing effects, should be considered.

Other interactions

A study involving healthy volunteers detected N-acetyl-S-allyl-L-cysteine (allylmercapturic acid) in their urine following ingestion of garlic tablets. As allylmercapturic acid is used as a biomarker for monitoring human exposure to allylhalides and other chemicals leading to allylmercapturic acid excretion, it was

suggested that garlic consumption may interfere with and confound this monitoring process.

Pregnancy and lactation

Garlic is reputed to act as an abortifacient and to affect the menstrual cycle, and is also reported to be utero-active.

In vitro uterine contraction has been documented. Studies have shown that consumption of garlic by lactating women alters the odour of their breast milk and the suckling behaviour of their infants. Further evidence for this comes from a blinded, placebo-controlled study involving 30 nursing women.The results indicated that infants who had no prior exposure to garlic odour in their mothers' milk spent more time breast feeding after their mothers ingested garlic capsules than did infants whose mothers had repeatedly consumed garlic.

Findings from a placebo-controlled study involving 10 healthy pregnant women undergoing routine amniocentesis indicate that the odorous components of garlic can be found in amniotic fluid following garlic consumption.

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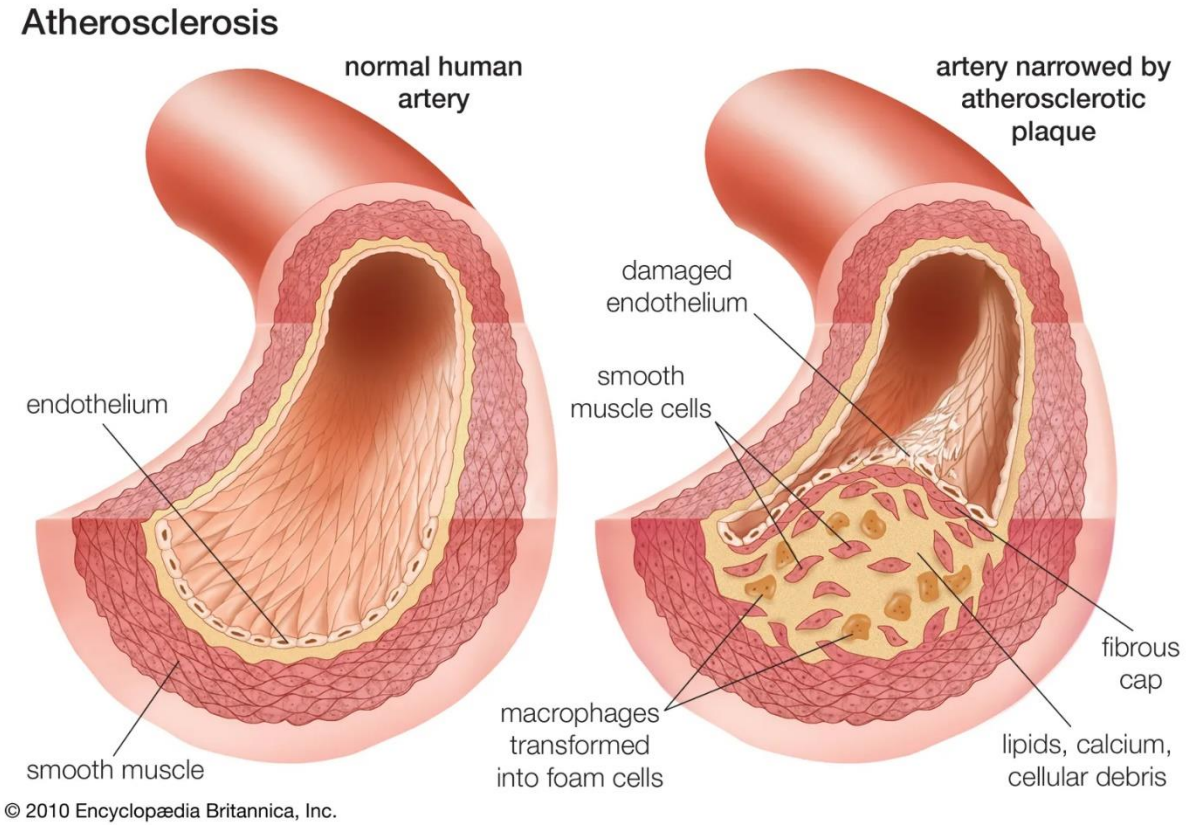
Plagiarism checking:

Arteriosclerosis



By

1-Khaled Nasser

2-David Magdy

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4-George Zakaria

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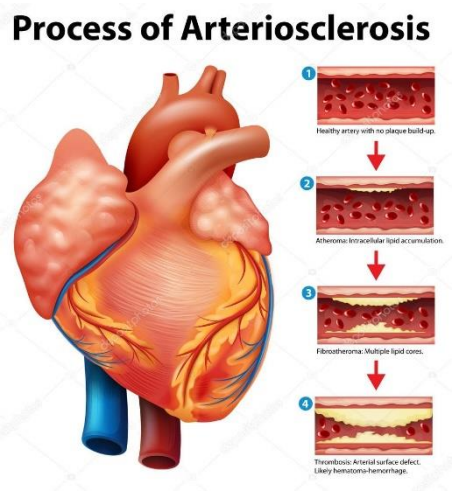
6-Shenoda Mekhael

7-John Nader

Index

Arteriosclerosis and **Atherosclerosis** are sometimes used interchangeably, but there is a distinction between the two terms. [1][2][3][4]



Arteriosclerosis happens when blood vessels (arteries) that transport oxygen and nutrients out from heart towards the rest of the body thicken and stiffen, sometimes restricting blood flow to organs and tissues.

Healthy arteries are flexible and versatile. Nevertheless, the artery walls can harden over time.

Atherosclerosis is a form of arteriosclerosis.

The accumulation of fats, cholesterol, and other substances within and on the artery walls is known as **Atherosclerosis**. This buildup is known as plaque. Plaque can prompt narrowing of the arteries, cutting off blood flow. Plaque rupture can occur, leading to a blood clot. It can be due to smoking, a poor diet, or a wide range of genetic factors.

If left untreated, **Atherosclerosis** can progress to a variety of serious conditions known as cardiovascular disease (CVD). Typically, there will be no symptoms until CVD develops., with both genetic and environmental factors playing a role. A long list of genetic and non-genetic risk factors for CVD has been identified in genetic-epidemiologic studies. Such studies, however, reveal that family history is the single most significant independent risk factor.

Types of CVD include:

- Coronary heart disease
- Angina
- Heart attacks
- Strokes
- Transient ischemic attacks (TIAs)
- Peripheral arterial disease

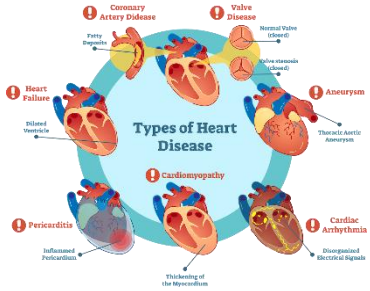
Risk factors: -

Arteriosclerosis develops over time. Arteriosclerosis is a major risk of ageing. Other factors that may increase the likelihood of atherosclerosis are as follows [1][3][4].

- A family history of heart disease at a young age

  When you have a family history of CVD, your chances of developing it are also higher.

  you are considered to have a CVD family history: -



- If either your father o r brother was diagnosed with CVD before the age of 55,
- Before the age of 65, your mother or sister was diagnosed with CVD.

  If you have a family history of CVD, tell your doctor or nurse. They may advise you to have your blood pressure and cholesterol levels checked.

- Unhealthy eating habits

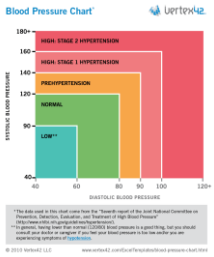
Foods high in saturated fats, salt, or sugar, or foods that may raise your blood Cholesterol such as fatty cuts of meat, lard, cream, cakes, and cookies may increase your risk.

- Diabetes

Diabetes is a chronic disease in which your blood sugar levels become abnormally high.
High blood glucose levels can damage blood vessels, increasing their likelihood of narrowing.
Numerous indi viduals who have type 2 diabetes are also

overweight or obese, which tends to increase their risk of CVD.

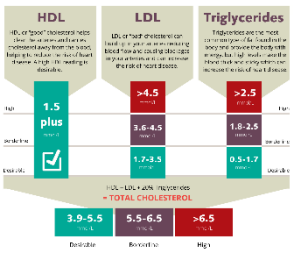
- Blood pressure is elevated.



One of the most important risk factors for CVD is high blood pressure (hypertension). Damage to Blood vessels may occur if your blood pressure is too elevated.

- High blood cholesterol

Cholesterol is a fat present in the blood. High cholesterol levels can cause blood vessels to constrict, increasing your risk of developing a blood clot.



- High levels of C-reactive protein (CRP), an inflammatory marker

- Ethnic background

Individuals from South Asian and Black African or African Caribbean ancestry are at a higher risk of developing CVD. This is due to the fact that people from such backgrounds are much more likely to have other CVD risk factors such as high blood pressure or type 2 diabetes.

- A lack of physical activity

If you don't exercise on a regular basis, you're more likely to have high blood pressure, high cholesterol, and also be overweight. These are all CVD major risk factor.

Regular exercise will help maintain a healthy heart. Workout, when combined with a healthy diet, can also assist you in maintaining a balanced weight.

- Overweight

Obesity and being overweight increase the likelihood of developing diabetes and high blood pressure, which are both major risk factor for CVD. You seem to be more likely to have CVD if you:

- If you have a 25 BMI or higher.
- You have a waist measurement of 94cm (about 37 inches) or more(male)
- A waist measurement of 80cm (about 31.5 inches) or more (female).

- Obstructive sleep problems

- Tobacco use, including smoking

Tobacco use, such as smoking, is also a major risk factor for cardiovascular disease. Tobacco contains dangerous substances that can harm and narrow your blood vessels

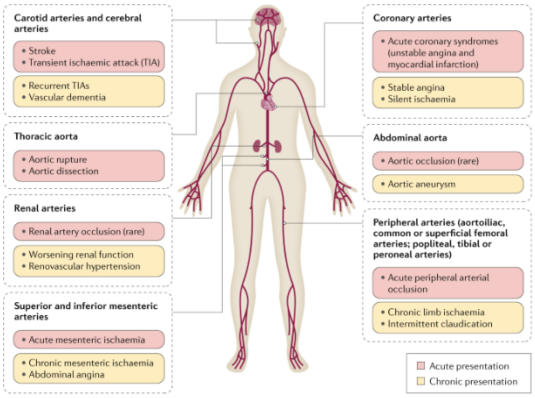
- Age

as the person grows older, the threat of arteriosclerosis rises, and genetic or lifestyle factors cause plaque to slowly build up in the arteries - by middle-age or older, enough plaque

o

has built up to cause signs or symptoms; in men, the risk rises after age 45, while in women, the risk rises after age 55.

Some of these factors are beyond your control, but by addressing issues such as an unhealthy lifestyle and a lack of physical activity you can help lower your risk of atherosclerosis and CVD.



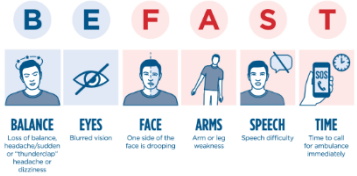
Signs and symptoms

Mild arteriosclerosis usually has no symptoms.

Symptoms of arteriosclerosis usually do not appear until an artery has become so narrowed or clogged that it cannot provide sufficient blood to tissues and organs. A blood clot can completely stop blood flow. The clot can rupture, leading to a heart attack or stroke.

The symptoms of mild to severe arteriosclerosis vary according to the arteries affected. For example [3][4] :

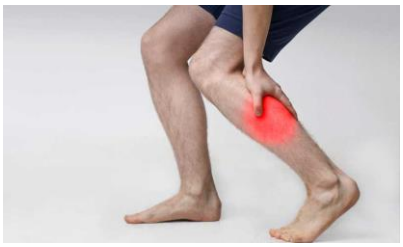
- You may experience chest pain, Shortness of breath or Arrhythmias (abnormal heartbeat) if you have atherosclerosis in your heart arteries (angina).



- You may experience sudden weakness or numbness in your legs or arms trouble speaking or slurred speech, temporary loss of vision in one eye,

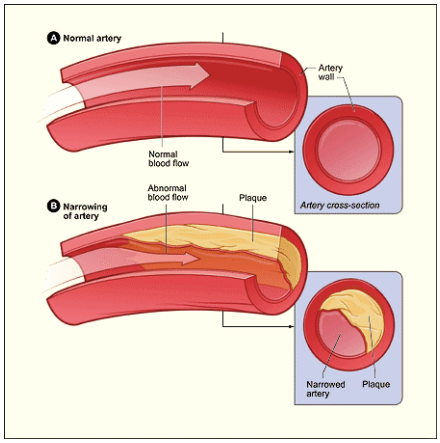
or droopy muscles in your face if you got atherosclerosis in the brain arteries. These symptoms indicate a transient ischemic attack (TIA). A TIA, if left untreated, can lead to a (stroke).

- If you suffer from atherosclerosis in your arteries in your arms and legs, you may experience symptoms of peripheral artery disease, such as leg pain when walking (claudication) or low blood pressure in an affected limb.

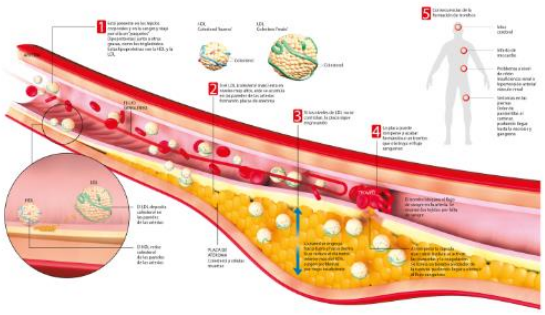


- You may suffer from high blood pressure or kidney failure if you have atherosclerosis in the arteries leading to your kidneys.

Pathophysiology [2][5]

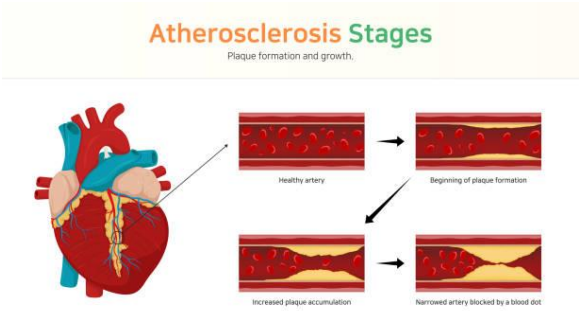


Arteriosclerosis (or atherosclerosis) is a major cause of disability or death, primarily affecting the vessels of the brain, heart, and kidneys. Kidney disease, high blood pressure, uremia, apoplexy, premature senility, angina pectoris, coronary heart disease, and coronary thrombosis are all complications of arteriosclerosis.



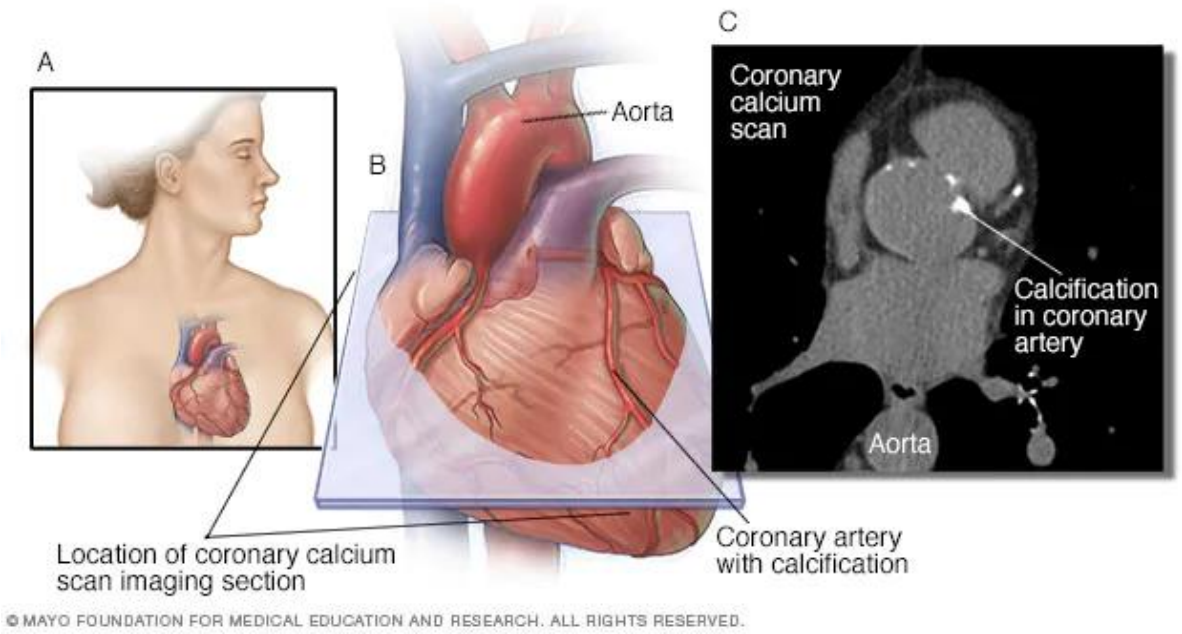
Hardening of the arteries, as well as other artery and vein diseases, can occur in the extremities. Coronary heart disease is the most common type of arteriosclerosis. This causes narrowing of the arteries carrying blood to the heart muscle or the formation of clots within their lumen,

both of which prevent bloodflow. Precautionary measures against arteriosclerotic vascular and heart disease are still in their infancy. Recent focused research has resulted in limited advances, such as the use of anticoagulant therapy in coronary thrombosis and other thrombo-embolic phenomena. Although this therapy deserves to be used more widely, many areas



lack the necessary facilities and personnel. Arteriosclerosis is an artery disease that mainly affects the intimal coat and is associated with increased lipid accumulations and fibrous thickening in specific areas of the intima. It is well known that individual lesions frequently coalesce and undergo further degenerative changes. Necrosis of the centers of arteriosclerotic lesions with the formation of cavities filled with lipid-rich debris (atheromata), the extension of the process to include the media, necrosis and disintegration of the intimal lining over atheromata, and calcification of the lesions are examples of further degenerative changes. These changes progress in the absence of recognized clinical signs or symptoms, or abnormalities detectable by current laboratory methods, until the disease has caused significant blood supply impairment. The disease's morbidity and mortality are primarily caused by the narrowing or occlusion of coronary, cerebral, or peripheral arteries caused by arteriosclerosis with or without thrombosis. The inability to study the lesion itself in a living patient, or to determine whether it is developing, regressing, or remaining static at any given time, makes studying the factors that may be involved extremely difficult. Sterols and their esters account for 85% to 90% of the lipids found in arteriosclerotic lesions. Phospholipids account for about 5% of the total, with neutral fats accounting for less than 4%. Approximately 60% of sterols are esterified with fatty acids. Even though cholesterol accounts for the majority of the sterol, small amounts of dihydrocholesterol and cholesterol

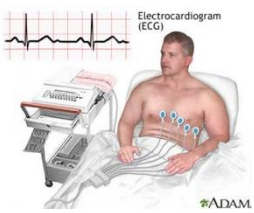
oxidation products are also present. These facts, along with some information on changes in mineral content during calcification of lesions and the relative amounts of elastin, collagen, and chondroitin sulfuric acid that accompany fibrosis, constitute the majority of the biochemical information that can be definitively linked to arteriosclerosis. Although direct evidence is lacking, it appears likely that the lipids in the lesions are derived from blood lipids. If it really is true, any factor which affects the chemical composition, level, stability, or physical state of lipids in the blood may play a role in disease pathogenesis. Arteriosclerosis develops earlier and more frequently in people with high blood cholesterol levels than in individuals who have normal blood cholesterol levels, although there is no proof that having high blood cholesterol levels is necessary for the development of arteriosclerosis in people. Although experimental arteriosclerosis is frequently induced in hypercholesterolemic animals, new evidence indicates that the absolute level of cholesterol in the blood is not the determining factor. On the contrary, it appears that the relationship of cholesterol to other substances in the blood is more important than its absolute amount. A low phospholipid cholesterol ratio is more closely linked to the development of experimental and human arteriosclerosis than hypercholesterolemia itself. The investigation of blood lipids in relation to the pathogenesis of arteriosclerosis has resulted in the neglect of other factors. It is unknown whether changes in endothelial permeability or the subendothelial ground substance influence lipid deposit. Almost nothing is known about the potential importance of lipid phagocytosis by lining endothelial cells or other cells in the subendothelial layer. Nothing is known about these cells' metabolic activities in relation to local lipid deposition. Variations in the structure and composition of the vessel wall itself, as well as mechanical or hydrodynamic forces that act at specific points in the arterial walls, can all influence the localization of arteriosclerotic lesions. Nevertheless, there is almost no reliable evidence regarding the relative importance of such localizing factors.



Diagnosis

Your doctor will conduct a physical examination and inquire about your family's and personal health history. You may be referred to a specialist in heart disease (cardiologist). When your practitioner listens to your arteries with a stethoscope, he or she may hear a whooshing sound (bruit). Depending on the findings of the physical exam, your doctor may recommend one or more tests, such as [1][3][4][6]:

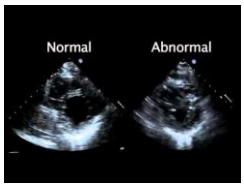
- Blood tests are performed. Blood tests are typically performed to assess cholesterol and blood sugar levels. High blood sugar and cholesterol levels increase the risk of atherosclerosis. A C-reactive protein (CRP) test can be done to search for a protein corelated to artery inflammation.



- Electrocardiogram (ECG or EKG) (ECG or EKG). The electrical activity of the heart is measured using this rapid and painless test. Sensors (electrodes) are attached to the chest and, in some cases, the arms or legs during an ECG. The sensors are linked by cords to a machine that displays or prints the

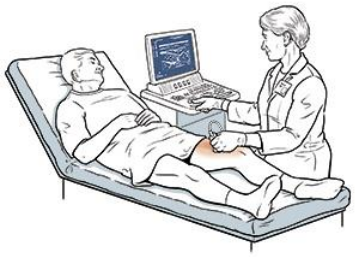
results. An ECG can help determine whether there is a decrease in the heart's blood flow.

- Exercise stress test. If your signs typically appear during exercise, your doctor may suggest this test. Your heart rate will be monitored as you walk on a treadmill or ride a stationary bike. Because exercise causes the heart to beat faster and harder compared to what happens during most everyday activities, an exercise stress test can detect heart problems that would otherwise go undetected. If you are unable to exercise, your doctor may prescribe a medication that resembles the exercise's effect on your heart.

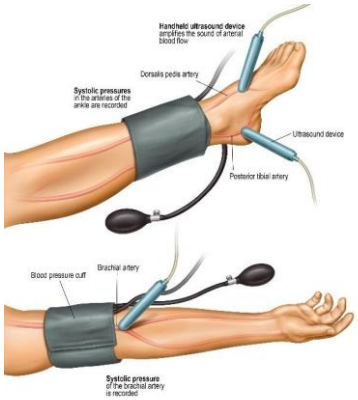


- Echo cardiogram. This test employs sound waves to demonstrate blood flow through the heart. Exercise stress testing is occasionally used with it.

- Doppler ultrasound. Your practitioner may use a Doppler ultrasound device to monitor your blood pressure at different points across your leg or arm. These readings can reveal the rate of blood flow through the arteries.

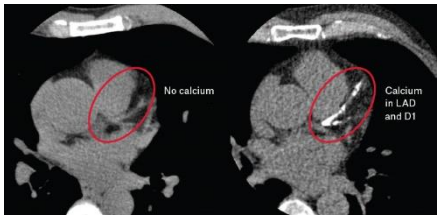


- Ankle-brachial index (ABI). This test is used to compare the blood pressure in the ankle to the blood pressure in the arm. It is performed to detect atherosclerosis in the arteries of the legs and feet. A difference in ankle and arm measurements could be the result of peripheral vascular disease, which is typically caused by atherosclerosis.



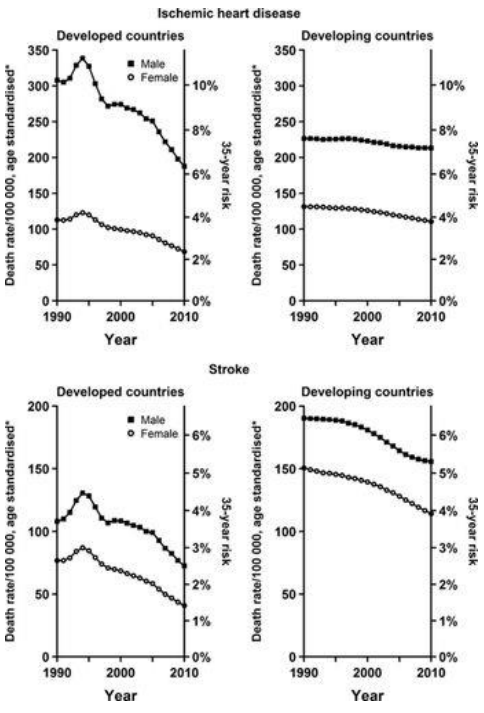
- Cardiac catheterization and angiogram. This test can determine whether the coronary arteries are narrowed or obstructed. A long, thin flexible

tube (catheter) is inserted in a blood vessel, usually in the groin or wrist, and guided to the heart. Dye is delivered to arteries in the heart via the catheter. The dye makes the arteries more visible on images taken during the test.



- Calcium scan of the heart. This test, also known as a heart scan, employs computerized tomography (CT) imaging to produce detailed images of the heart. It can show calcium deposits in the artery walls. The test results are given as a score. The more elevated the score when calcium is present, the greater the risk of heart disease.
- Other imaging studies. The arteries can also be studied using magnetic resonance angiography (MRA) or positron emission tomography (PET). These tests can reveal artery hardening and shrinking, as well as aneurysms.

Epidemiology [7]



Because arteriosclerosis is primarily asymptomatic, determining the occurrence precisely is incredibly hard. Atherosclerosis is widely regarded as the leading cause of coronary heart disease. Ischemic heart disease (IHD) and ischemic stroke are the most common forms of atherosclerotic cardiovascular disease. IHD and stroke are the world's first and fifth most common causes of death.

Every year, approximately 610,000 individuals across the United States pass away as a result of cardiovascular disease. That

corresponds to one out of every four deaths. Coronary heart disease is the most common cause of death in the Western world, claiming the lives of above 370,000 people each year. Each year, approximately 735,000 Americans have a cardiac arrest. 525,000 have an initial attack, and 210,000 have recurring attacks. It has been revealed that plaque rupture causes 75% of acute myocardial infarctions, with men over 45 years having the highest occurrence, while women have a higher frequency after the age of 50. This increased incidence of arteriosclerosis in men to women is due to the protective function of female sex hormones, which is lost after menopause.

Prevention

The same healthy changes in lifestyle that are recommended to treat atherosclerosis also aid in its prevention. These lifestyle changes can aid in artery health[1][4]:

- Smoking cessation
- Consuming nutritious foods
- Regular physical activity
- Keeping a healthy weight
- Keeping track of and maintaining a healthy blood pressure
- Monitoring and maintaining normal cholesterol and blood sugar levels

Treatments

Treatment for arteriosclerosis may only require changes in lifestyle such as eating a nutritious diet and engaging in physical activity. However, medication or surgical procedures may be required at times [1][3][4][8].

Medications

There are numerous medications available to slow or perhaps even reverse the results of arteriosclerosis. The following drugs are used to treat atherosclerosis:

- ACE inhibitors and beta blockers decrease blood pressure and the workload on the heart.
- Anti-platelet or anti-clotting medications may assist individuals with arteriosclerosis reduce their complications risk. Most individuals should refrain from taking aspirin.
- Calcium channel blockers work by easing blood vessels to lower blood pressure.
- Blood sugar control medications, such as empagliflozin, canagliflozin, and liraglutide, can help reduce your risk of problems if you have atherosclerosis and diabetes.
- If you have diabetes, metformin can assist you in preventing plaque buildup.
- Nitrates, including such nitroglycerin, dilate your coronary arteries, relieving or preventing angina chest pain.
- Ranolazine is used to treat coronary microvascular disease and the associated chest pain.
- Statins are medications that are used to treat high levels of blood cholesterol. If you are between the ages of 40 and 75 and have a higher risk of coronary heart disease or stroke, or if you suffer from diabetes, your physician may advise you to take a statin.
- Other cholesterol-lowering meds, like ezetimibe, a PCSK9 inhibitor, bempedoic acid, and omega-3 fatty acids, may be taken if you aren't able to take statins or if statins haven't been effective in treating high blood cholesterol and triglyceride levels.
- Thrombolytic medications, also known as clot busters, could be used to treat blood clots caused by atherosclerosis. These medications have the capability to dissolve blood clots that halt arteries, resulting in a stroke,

heart attack, mesenteric Ischemia, or other complications. Preferably, the medication should be administered as soon as possible.

Surgery or other procedures

A more aggressive approach to treating atherosclerosis is sometimes required. If your symptoms are serious or you have a blockage, you may require a procedure or surgical intervention, such as:

- Angioplasty and stent placement. This operation, also known as percutaneous coronary intervention (PCI), aids in the opening of an obstructed or halted artery. A catheter is a long, thin, flexible tube that is inserted into a blood vessel, usually in the groyne or wrist, and guided to the blockage. The artery can then be opened by inflating a balloon on the tip of a catheter. To maintain the artery open, a mesh tube (stent) is typically used.
- Endarterectomy. Procedure sometimes is necessary to remove plaque from the walls of a narrowed artery. A carotid endarterectomy is a procedure that is performed on the arteries in the neck (the carotid arteries).
- CABG stands for coronary artery bypass graft surgery. A healthy blood vessel from another part of the body is used by a surgeon to establish a new path for blood through the heart. The blood then circulates around the blocked or narrowed coronary artery. CABG is an open-heart procedure. It is typically reserved for people who have a lot of narrowed heart arteries.
- Fibrinolytic treatment. If a clot in an artery is obstructing blood flow, your doctor may use a clot-dissolving medication to break it up.

Table 1 – Modification of lipoprotein levels.

Plant Name	Family	Part of plant	Active Constituents	Dose	Model used	Positive Control	Inference
Aegle marmelos (Linn.) (Vijya et al., 2009)	Rutaceae	Leaves	Skimmianine, Aegeline, Lupeol, Cineol, Citral, Citronella, Cuminaldehyde, Eugenol, Marmesinine	125 and 250 mg/kg (p.o) 50% Ethanolic extract	Triton WR 1339 induced hyperlipidemia in Wistar albino rats	Atorvastatin (1 mg/kg; p.o.) Gemfibrozil (50 mg/kg; p.o)	Attenuated serum TC and TG with an increase in HDL
Apium graveolens Kamal et al., 2009	Apiaceae	Seeds	Flavonoids, coumarins, and terpenoids	213 or 425 mg/kg (p.o) Ethanolic extract	Hypercholesterolemic diet induced dyslipidemia in male albino rats	–	Significant decrease of serum total cholesterol, TG, LDL and significant increase in HDL
Brassica juncea (Avery and Mahua, 2011)	Brassicaceae	Seeds	Erucic acid	20% MCTM and 20% PUFAM	Hypercholesterolemic male albino rats	–	Hypocholesterolemic and hypolipidemic effects with increase in HDL level
Carica papaya L. (Iyer et al., 2011)	Caricaceae	Fruit	Papain (proteolytic enzyme), tannins, alkaloids, glycosides	Oral doses of 200 and 400 mg/kg body weight ether and water soluble fractions of ethanolic extract	Olive oil-induced hyperlipidemic rats	–	Inhibited TC,TG, LDL levels, and significantly increased HDL level
Cassia auriculata (Shipra et al., 2009)	Fabaceae	Leaves	Alkaloid, flavonoid, Saponin, tannins, cardiac glycosides, phenols	100, 200, 400, 600 mg/ kg body weight daily for 21 days (p.o) Aqueous and ethanolic extracts	Alloxan induced mild and severe diabetes	Glibenclamide	Increased level of insulin, decreased plasma levels of TG, TC and LDL, increased HDL levels
Cassia tora (Umesh and Patil, 2004)	Fabaceae	Seeds	Anthraquinone, beta-sitosterols	Ethanolic extract	Triton induced hyperlipidemia	–	Reduction in LDL and TC levels
Cinnamomum zeylanicum Blume (Khaled and Moattar, 2015)	Lauraceae	Bark	Monoterpenoids and phenyl propanoids	200 mg/kg (p.o) Ethanolic extract	Streptozotocin induced diabetes mellitus	–	Significant elevation in HDL level and decrease in total cholesterol, triglycerides and LDL levels
Cyamopsis tetragonoloba (Todd et al., 2006)	Fabaceae	Seeds	Gum (polysaccharide)	Seed powder	Pigs fed on Atherogenic diet	–	Reduction in hepatic free cholesterol concentration; increased SREBP2 expression and hepatic LDL receptor abundance
Cynara scolymus, (Lupattelli et al., 2004)	Asteraceae	Leaves	Flavonoids (luteolin)	20 ml/die of frozen artichoke juice (p.o)	Isocaloric-hypolipidic diet induced endothelial dysfunction	–	Significant reduction in total and LDL level
Eclipta prostrate (L.) L. (Dhandapani, 2007)	Asteraceae	Leaves	Beta-amyrin, wedelolactone, triterpenoids, flavonoids, leutiolin-7-o-glucoside, stigmasterol, l-terthenyl methanol	100 and 200 mg/kg (p.o) Aqueous extract	Atherogenic diet induced hyperlipidemia in rats	–	Significant reduction in TC, TG and elevation of HDL level
Embelia ribes Burm (Uma et al., 2002)	Myrsinaceae	Fruit	Embelin, Embeliol	200 mg/kg (p.o) Ethanolic extract	Streptozotocin induced diabetes in Wistar rats	Gliclazide (25 mg/kg, orally)	Decrease in blood glucose, serum TC, TG and increase in HDL levels
Emblica officinalis (Antony et al., 2006)	Euphorbiaceae	Fruit	Flavonoids emblicanin-A- and emblicanin-B-	10 and 20 mg/kg (p.o) Methanolic extract	Cholesterol diet induced hypercholesterolemia in NZ white rabbits	–	Inhibition of HMG CoA reductase activity and elevating HDL level to enhance reverse cholesterol transport

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Table 1 – (continued)

Plant Name	Family	Part of plant	Active Constituents	Dose	Model used	Positive Control	Inference
Ficus carica L. (Lorenz et al., 2014)	Moraceae	Leaves	Phytosterols, organic acids, anthocyanin composition, triterpenoids, coumarins	50 mg/kg or 100 mg/kg	High fat diet induced hyperlipidemia in Male Sprague-Dawley rats	Pioglitazone 30 mg/kg (p.o)	Improved the lipid profile and decreased adipogenic risk factors through an increase in HDL levels
Ficus virens Ait (Danish et al., 2015)	Moraceae	Bark	Saponin, alkaloid, tannins, sterols	100 mg/kg (p.o) Methanolic extract	Triton WR-1339-induced hyperlipidemic rats	Atorvastatin 10 mg/kg (p.o)	Altered levels of lipoproteins, and inhibition of hepatic HMG-CoA reductase activity
Lagenaria siceraria (Mol.) Stand. (Mithun et al., 2014)	Cucurbitaceae	Fruit	Flavonoids, triterpenoids, pectins, sterols	200 and 400 mg/kg (p.o) Ethanolic extract	Atherogenic diet induced hypercholesterolemia in albino Wistar rats	Atorvastatin 10 mg/kg (p.o)	Ameliorated the atheromatous lesions by modulating HMG-CoA reductase and lipoprotein lipase enzymes activity
Lagenaria siceraria (Mol.) Stand. (Ghule et al., 2006)	Cucurbitaceae	Fruit	Flavonoids, sterols, cucurbitacin saponins and polyphenolics	200 and 400 mg/kg body weight (p.o) Petroleum ether, alcoholic, aqueous and chloroform extracts	Triton induced hyperlipidemia in rats	–	Antihyperlipidemic activity via lowering of LDL, TC, TG and increased levels of HDL levels
Medicago sativa (Dixit and Prabha, 1990)	Leguminosae	Seeds	TRH and Saponin	Ethanolic extract	High fat diet induced atherosclerosis in rabbits	–	Decrease in the serum total cholesterol, triglyceride, phospholipids, LDL and VLDL
Musa paradisiacal (Chhanda et al., 2006)	Musaceae	Root	Rutin, norepinephrine, lignin	80 mg/0.5 mL olive oil/ 100 g body weight/rat/ day for 14 days Methanolic extract	Streptozotocin-induced diabetes in Wistar strain male albino rats	–	Significant decrease in LDL and increase HDL serum level
Passiflora foetida L. (Ravi et al., 2016)	Passifloraceae	Leaves	Glycosides, flavonoids	100, 250, 500 mg/kg (p.o) Ethanolic extract	Dextrose induced diabetes mellitus	Glipizide, Sitagliptin and Vildagliptin	Significant decrease in total cholesterol, triglycerides, LDL, VLDL levels
Persea Americana (Brai et al., 2007)	Lauraceae	Leaves	Persenone A and B	10 mg/kg of body weight aqueous and methanolic leaf extracts	High fat diet induced hypercholesterolemia in Albino rats	–	Lowers plasma glucose and influence lipid metabolism with consequent lowering of TC, LDL and restoration of HDL levels
Polyalthia longifolia var. pendula, (Koneni et al., 2011)	Annonaceae	Leaves	Diterpenes	500 mg/kg body-wt Ethanolic extract	High fat diet induced dyslipidemia in hamsters	Lovastatin at the dose of 25 mg/kg body-wt	Reversal of dyslipidemia by inhibition of HMG -CoA reductase activity
Symplocos racemosa Roxb. (Durkar et al., 2014)	Symplocaceae	Bark	Flavonoids, phenolic glycosides, alkaloids, triterpenoids, steroids	200 and 400 mg/kg (p.o) Ethanolic extract	Triton WR 1339 and high fat diet induced hyperlipidemia in male Sprague Dawley rats	Simvastatin 10 mg/kg p.o	Exhibited antihyperlipidemic activity via inhibition of HMG-CoA reductase; Antioxidant activity
Terminalia arjuna (Saravanan et al., 2011)	Combretaceae	Bark	Phenolics compounds, tannins, glycosides, saponins, alkaloids and flavonoids	100 and 200 mg/kg (p.o) Ethanolic extract	High fat diet induced atherogenesis in rabbits	Atorvastatin	Hypolipidemic, elevated HDL and induced partial inhibition of aortic atherosclerosis
Viscum album (Oluwatosin et al., 2012)	Santalaceae	Excudate	Alkaloids, cardenolides, anthraquinones, saponins and tannins	50 mg/kg and 100 mg/kg Methanolic extract	Hyperlipidemia in streptozotocin-induced diabetic rats.	Glibenclamide	Decreased levels of serum triglyceride, urea, lactate dehydrogenase, α-amylase and LDL; increased levels of HDL levels
Viscum album (Ben et al., 2006)	Santalaceae	Leaves	Alkaloids	200 mg/kg body weight orally and daily Aqueous extract	Hypercholesterolemic male Wistar rats	–	Increased HDL levels

Table 2 – LDL oxidation.

Plant Name	Family	Part of plant	Active Constituents	Dose	Model used	Positive Control	Inference
Aframomum melegueta (Samuel et al., 2014)	Zingiberaceae	Seeds	Mono and Sesquiterpenes	100, 200 and 400 mg/kg dose Methanolic extract	In vivo oxidative stress in male albino Wistar rats	–	Elevated the antioxidant enzyme
Allium sativum (Hassan et al., 2010)	Alliaceae	Fruit	Polyphenolic compounds and phytosterols	Homogenate of garlic (100 mg/kg) orally	Cholesterol-containing diet induced atherosclerosis in pregnant rats and their offspring	–	Antihyperlipidemic and antioxidant
Brassica oleracea (Sankhari et al., 2012)	Brassicaceae	Fruit	Anthocyanins, alkaloids, tannins, saponins, phenols, glycosides, steroids, terpenoids and flavonoids	100 mg/kg of body weight	Atherogenic (ATH) diet-induced hypercholesterolemia in rats	–	Prevented elevation in serum and tissue lipids and attenuation of cardiac and hepatic antioxidants and lipid peroxidation
Cassia auriculata (Vijayaraj et al., 2011)	Fabaceae	Flowers	Flavonoids, sitosterol, d-glucoside, polysaccharides, anthracene and myristyl alcohol	150, 300, 450 mg/kg b.w./day Ethanolic extract	Triton WR 1339 induced hyperlipidemia	Lovastatin	Antihyperlipidemic and antioxidant
Curcuma longa (Quiles et al., 2002)	Zingiberaceae	Rhizomes	Bis-demethoxy-curcumin, demethoxy-curcumin, and Curcumin	Hydroalcoholic extract	High cholesterol diet induced atherosclerosis in rabbits	–	Reduction of oxidative stress and attenuation of the development of fatty streaks
Curcuma longa (Jingjing et al., 2012)	Zingiberaceae	Rhizomes	Terpinolene, b-Caryophyllene, Curcumene, Zingiberene, b-Bisabolene, b-Sesquiphellandrene, a-Turmerone, b-Turmerone	100 and 300 mg/kg of body weight (p.o) Turmeric oil	High fat diet induced hyperlipidemia in male Sprague Dawley rats	Xuezhikang	Anti-hyperlipidemic and antioxidant
Cynara scolymus (Küskü-Kiraz et al., 2010)	Asteraceae	Leaves	Caffeoylquinic acid derivatives (cynarine and chlorogenic acid) and flavonoids (luteolin, apigenin)	1.5 g/kg/day (p.o)	High cholesterol diet induced hypercholesterolemia and lipid peroxidation	–	Prevention of hypercholesterolemia-induced pro-oxidant state in LDL + VLDL fraction and the reduction of increased serum cholesterol and triglyceride levels
Emblica officinalis (Antony et al., 2006)	Euphorbiaceae	Fruit	Flavonoids emblicanin-A- and emblicanin-B-	10 and 20 mg/kg (p.o) Methanolic extract	Cholesterol diet induced hypercholesterolemia in NZ white rabbits	–	Reversal of dyslipidemia and atheromatous plaques by prevention of LDL oxidation

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Table 2 – (*continued*)

Plant Name	Family	Part of plant	Active Constituents	Dose	Model used	Positive Control	Inference
Ipomoea batatas L. (Miu et al., 2011)	Convolvulaceae	Leaves	Polyphenols (caffeoylquinic acid)	18 g of raw leaves	Lag time, TBARS products and LDL mobility determination test	–	Inhibition of LDL oxidation
Punica granatum (Michael et al., 2008)	Punicaceae	Peels, Arils, seeds and Flowers	Phenolics (punicalagin, punicalin, gallic acid, and ellagic acid	200 μg of gallic acid equivalents (GAE)/mouse/day	Assessment of atherosclerosis in Apolipoprotein E-Deficient (E^0) Mice and Cultured Macrophages and lipoproteins	–	Attenuation of atherosclerosis by decrement in serum cholesterol level together with a significant inhibition in macrophage uptake of ox-LDL and in cellular cholesterol biosynthesis rate
Punica granatum (Marielle et al., 2001)	Punicaceae	Whole fruit	Polyphenolic flavonoids like anthocyanins, catechins, ellagic, tannins, gallic and ellagic acids	31 mL of fruit juice per day; oral route	Serum cholesterol, lipid peroxidation and paraoxonase (arylesterase) activity	–	Reduction in macrophage lipid peroxidation, cellular cholesterol accumulation and atherosclerotic development
Scutellariae baicalensis (Kim et al., 2015)	Lamiaceae	Roots	Baicalein, wogonin, neobaicalein, and skullcapflavone	Dried root extract	LDL oxidation and inflammation in macrophages	–	Inhibition of LDL oxidation
Sesamum indicum Linn (Nishant et al., 2009)	Pedaliaceae	Seeds	Lignans-sesamol, sesamolinol, pinoresinol, sesaminol, vitamin-E	Aqueous and ethanolic extract	Lipid peroxidation and Copper-mediated LDL oxidation in vitro	–	Protection against LDL oxidation
Vitis vnifera (Bianca et al., 2005)	Vitaceae	Fruit	Flavanols, Anthocyanins, Quercetin, Myricetin, Kaempferol, Resveratrol	150 μg total polyphenols/day in the form of grape powder	Assessment of atherosclerosis in Apolipoprotein E-Deficient (E^0) Mice	–	Anti-atherosclerotic effect by reducing macrophage-mediated oxidation of LDL and cellular uptake of oxidized LDL.
Zingiber officinale Roscoe (Fuhrman et al., 2000)	Zingiberaceae	Rhizomes	Gingerol, zingerone, shogaols	5 mg of ginger extract/d in 1.1% alcohol and water	Atherosclerosis in apolipoprotein E-deficient (E^0) mice	–	Attenuates the development of atherosclerotic lesions via reduction in plasma and LDL cholesterol levels and a significant reduction in the LDL basal oxidative state, as well as their susceptibility to oxidation and aggregation

Table 3 – Endothelial cell dysfunction and adhesion of molecules.

Plant Name	Family	Part of plant	Active constituents	Dose	Model used	Positive Control	Inference
Andrographis paniculata (Shen et al., 2013)	Acanthaceae	Leaves	Diterpenoids (andrographolide and neoandrographolide)	100 mg/kg dosage	Hyperlipidemic mice induced by 75% yolk emulsion and in hyperlipidemic rats induced by high fat emulsion	–	Hypolipidemic effects and cardiovascular protection via down-regulation of iNOS expression and up-regulation of eNOS expression
Camellia sinensis (Minatti et al., 2012)	Theaceae	Leaves	Xanthine derivatives	50, 100, or 300 mg/kg once a day by gavage (100 μL/10 g weight)	Hypercholesterolemic diet for atherosclerosis progression in homozygous knockout low-density lipoprotein receptor mice	–	Decrease in atherosclerosis progression by reversing endothelial dysfunction
Cynara scolymus (Graziana et al., 2004)	Asteraceae	Leaves	Flavonoids (luteolin)	20 mL/die of frozen artichoke juice (p.o)	Isocaloric-hypolipidic diet induced endothelial dysfunction	–	Reduction of VCAM-1 and ICAM-1
Gardenia jasminoides (Tang et al., 2006)	Rubiaceae	Fruits	Crocetin	(15, 30 mg/kg) p.o	Hypercholesterolemic rabbit	–	Restoration of EDR (Endothelium-dependent relaxation) of thoracic by increasing the vessel eNOS activity, leading to elevation of NO production.
Linum usitatissimum (Raluca et al., 2013)	Linaceae	Seeds	α-linolenic acid, lignan	15 g/100 g of food	Rats fed on a high-fat diet	–	Prevent leukocytes and platelets adhesion to endothelial cells and to reduce soluble adhesion molecules (sVCAM-1) and endothelial integrity markers (vWF)
Linum usitatissimum (Dupasquier et al., 2006)	Linaceae	Seeds	α-linolenic acid, lignin, PUFA	10% flaxseed-supplemented diet	Hypercholesterolemic conditions in New Zealand White rabbits	–	Attenuation of cholesterol-induced atherogenesis as well as abnormalities in endothelial-dependent vaso-relaxation
Punica granatum (Filomena et al., 2007)	Punicaceae	Whole fruit	Polyphones (punicalagin)	30–50 μL/day Extract diluted with water	Determination of cGMP and NOSIII bioactivity	–	Increased eNOS expression in endothelial cells
Scutellariae baicalensis (Kim et al., 2015)	Lamiaceae	Roots	Baicalein, wogonin, neobaicalein, and skullcapflavone	Dried root extract	LPS-induced RAW264.7 cells	–	Significant inhibition of NO production and iNOS expression
Vitis venifera (Jiang et al., 2015).	Vitaceae	Seeds	Proanthocyanidin	Proanthocyanidin extract	High glucose-induced increased levels of ICAM-1 and VCAM-1	–	Significant lowering of VCAM-1 and ICAM-1 levels via inhibition of NF-κB

Table 4 – Inflammatory process and smooth muscle cells migration and plaque formation.

Plant Name	Family	Part of plant	Active constituents	Dose	Model used	Positive Control	Inference
Cudrania tricuspidata (Carr.) (Ki Hun et al., 2006)	Moraceae	Root bark	Catecholic xanthones and flavonoids	–	LDL oxidation in TBARS assay	–	Anti-atherosclerotic and anti-inflammatory
Ruta graveolens L. (Raghav et al., 2006)	Rutaceae	Whole plant	Rutin	100–500 μg/mL methanol extract and rutin (20, 40 and 80 μM) for 2 hours	Murine macrophage cells (J-774) challenged with lipopolysaccharide (LPS)	–	Inhibitory effect on upregulation of iNOS and COX-2 enzymes
Xylopia aromatica (Lam.) Mart (Verena et al., 2014)	Annonaceae	Fruit	Alkaloids, flavonoids	Ethanolic extract	Inflammatory dysfunction induced by high refined carbohydrate-containing-diet in mice	Rutin (5, 10, 20, 30 and 40 μg/mL)	Attenuated glucose resistance and liver inflammation

Table 5 – Miscellaneous.

Plant Name	Family	Part of plant	Active constituents	Dose	Model used	Positive Control	Inference
Cajanus cajan (Luo et al., 2008)	Fabaceae	Seeds	Pinostrobin, quercetin, vitexin and cajanin stilbene acid	200 or 100 mg/kg Stilbene extract	Diet-induced hyperlipidemia in Kunming mice	Simvastatin	Hypocholesterolemic activity by enhancement of mRNA expressions of hepatic CYP7A1 and LDL-receptor.
Capsicum annum L. (Kwon et al., 2003)	Solanaceae	Fruit	Capsaicin	1% red pepper powder	Atherosclerosis in cholesterol-fed rabbits	–	Attenuated atherosclerosis and plasma CETP activity
Capsicum annum L. (Gupta et al., 2002)	Solanaceae	Fruit	Oleoresin	75 mg/kg body weight/day Methanolic extract	Atherogenic diet induced hypercholesterolemia in male gerbils	–	Reduced progression of hypercholesterolemia by increasing lipid excretion in fecal matter
Emblica officinalis (Antony et al., 2006)	Euphorbiaceae	Fruit	Flavonoids emblicanin-A- and emblicanin-B-	10 and 20 mg/kg (p.o) Methanolic extract	Cholesterol diet induced hypercholesterolemia in NZ white rabbits	–	Reversal of dyslipidemia and atheromatous plaques by prevention of LDL oxidation, by inhibition of HMG CoA reductase activity and elevating HDL level to enhance reverse cholesterol transport
Glycyrrhiza glabra (Choi et al., 2007)	Fabaceae	Root	Glabrol, isoprenyl flavonoid	Ethanolic extract	Rat liver microsomal ACAT activity	–	Inhibited rat liver microsomal ACAT activity and decreased cholesteryl ester formation in HepG2 cells along with a non-competitive type of inhibition against ACAT

Musa paradisiaca (Hamendra and Anand, 2007)	Musaceae	Fruit peel	Dopamine	100 mg/kg (p.o) Aqueous extract	Hypercholesterolemic diet-induced atherosclerosis	–	Hypolipidemic and anti-atherosclerotic with an alleviative role on thyroid dysfunctions and glucose homeostasis
Punica granatum (Hamendra and Anand, 2007)	Punicaceae	Fruit peel	Flavonoids, polyphenols	200 mg/kg (p.o) Methanolic extract	Hypercholesterolemic diet-induced atherosclerosis	–	Hypolipidemic and anti-atherosclerotic with an alleviative role on thyroid dysfunctions and glucose homeostasis
Scutellaria baicalensis Gerogi (Bak et al., 2014)	Lamiaceae	Root	Wogonin (Flavonoid)	Oral dose of Wogonin	db/db mice	–	Glucose and lipid metabolism related to enhanced PPARα and adiponectin expression via AMPK activation
Solanum lycopersicum (Fuiwara et al., 2012)	Solanaceae	Fruit	Tomatidine		Assessment of atherosclerosis in Apolipoprotein E-Deficient (E^0) Mice	–	Reduction of atherogenesis via suppression of ACAT-1 and ACAT-2
Solanum lycopersicum (Fujiwara et al., 2007)	Solanaceae	Fruit	Esculeoside A, Esculeogenin A	50 and 100 mg/kg/d	Assessment of atherosclerosis in Apolipoprotein E-Deficient (E^0) Mice	–	Reduction of atherogenesis via suppression of ACAT-1 and ACAT-2

Aegle marmelos

Apium graveolens

Brassica juncea

Carica papaya

Cassia tora

Cinnamomum

Cyamopsis

Cynara scolymus

Ficus carica L

Lagenaria siceraria

Medicago sativa

Persea Americana

Symplocos racemose

Allium sativum

Curcuma longa

Emblica officinalis

Punica granatum

Ipomoea batatas L

Vitis vinifera

Zingiber officinale

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DYSPEPSIA

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Contents

1 Introduction

Dyspepsia isn't a diagnosing however a set of symptoms as well as upper abdominal discomfort, heartburn, retrosternal pain, anorexia, nausea, vomiting, bloating, fullness, and early repletion Prevalence within the Western societies is quoted at being between 23 - 41%[1]

- 4% of GP consultations are for dyspepsia
- 10% of these are referred to hospital
- 15-20% of general population in the Western countries experience dyspepsia over the course of 1 year
- 1 in 4 people with dyspeptic symptoms choose to go to a physician
- 2% of entire adult population receive either an OGD or a barium meal each year

*Functional Dyspepsia often associated with chronic and intermittent symptoms[2]

- > 75% of patients have aggravation of symptoms after meals
- Accounts for 50-60% of all dyspepsia.
- 40 to 60% of patients with dyspepsia evaluated via EGD will have normal findings

2 Definition

Dyspepsia is defined as the presence of one or more of indigestion symptoms that are considered to originate from the gastroduodenal area

One or more of the following symptoms:

1. Post prandial fullness
2. Early Satiety

3. Epigastric pain

4. Epigastric Burning

3 Causes

Causes of the dyspepsia can be classified into internal and external causes[3-5]

- **Internal causes**:

  congenital causes like insufficiency of stomach tissue, a small size stomach, stomach ulcer and inflammation, brain disorder, inefficient abdominal membrane lining, liver disorder, and stomach malfunction.

- **External causes:**

  unhealthful drinking water, chronic mental disorders, wrong eating habits, inappropriate posture, or body movements and air pollution.

4 Symptoms

According to Rome III diagnostic or supportive symptoms, the symptoms of dyspepsia are as follow [6, 7]:

*Signs and Symptoms (n= x, %)

• Bloating (n=42, 93.3%)

• Stomach pain (n=40, 88.9%)

• Early satiety (n=36, 80.0%)

• Nausea (n=33, 73.3%)

• Burping (n=31, 68.9%)

• Upper abdominal burning (n=25, 55.6%)

• Postprandial fullness (n=21, 46.7%)

• IBS-like lower gastrointestinal symptoms

• Flatulence (n=12, 26.7%) • Diarrhea (n=9, 20.0%)

• Constipation (n=6, 13.3%)

• Urgency for bowel movement (n=1, 2.2%)

• GERD-like symptoms

• Acid reflux (n=23, 51.1%)

• Difficulty swallowing (n=4, 8.9%)

• Acid stomach (n=2, 4.4%)

• Other dyspeptic symptoms

• Cramps (n=15, 33.3%)

• Vomiting (n=13, 28.9%)

• Stomach growling (n=2, 4.4%)

• Other symptoms

• Hot flash (n=3, 6.7%)

• Fatigue (n=1, 2.2%)

5 Diagnosis

According to Dx criteria and subtypes, functional dyspepsia is diagnosed by[7, 8]

Presence of at least 1 of the following 4 symptoms [a, b],

Postprandial distress syndrome (symptoms at least 3 d/wk.)

1. Postprandial fullness, and/or

2. Early satiation

Epigastric pain syndrome (symptoms at least 1 d/wk[c])

3. Epigastric pain, and/or

4. Epigastric burning

a Criteria consummated for the last three months, with symptom onset a minimum of six months before diagnosis.

b No evidence of organic, systemic, or metabolic disease likely to explain the symptoms on routine investigations (including upper endoscopy).

c Severe enough to interfere with daily activities.

6 Complications

There are 3 important complications associated with dyspepsia as follows[9]:

Esophageal stricture

This complication results from persistent exposure to stomach acid which lead to scarring in the upper gastrointestinal tract. So, the tract may become narrower and constricted, this leads to difficulty in swallowing and chest pain.

Treatment: surgery to increase the width of esophageal diameter.

Symptoms of it: Difficulty swallowing, food becoming lodged in the throat and chest pain

Pyloric stenosis

The pylorus is that the passage between the stomach and the small intestine. Long term irritation of pylorus will be done by stomach acids, thus it causes scarring and narrowing of pylorus.

Treatment: surgery is necessary to return the width of pylorus

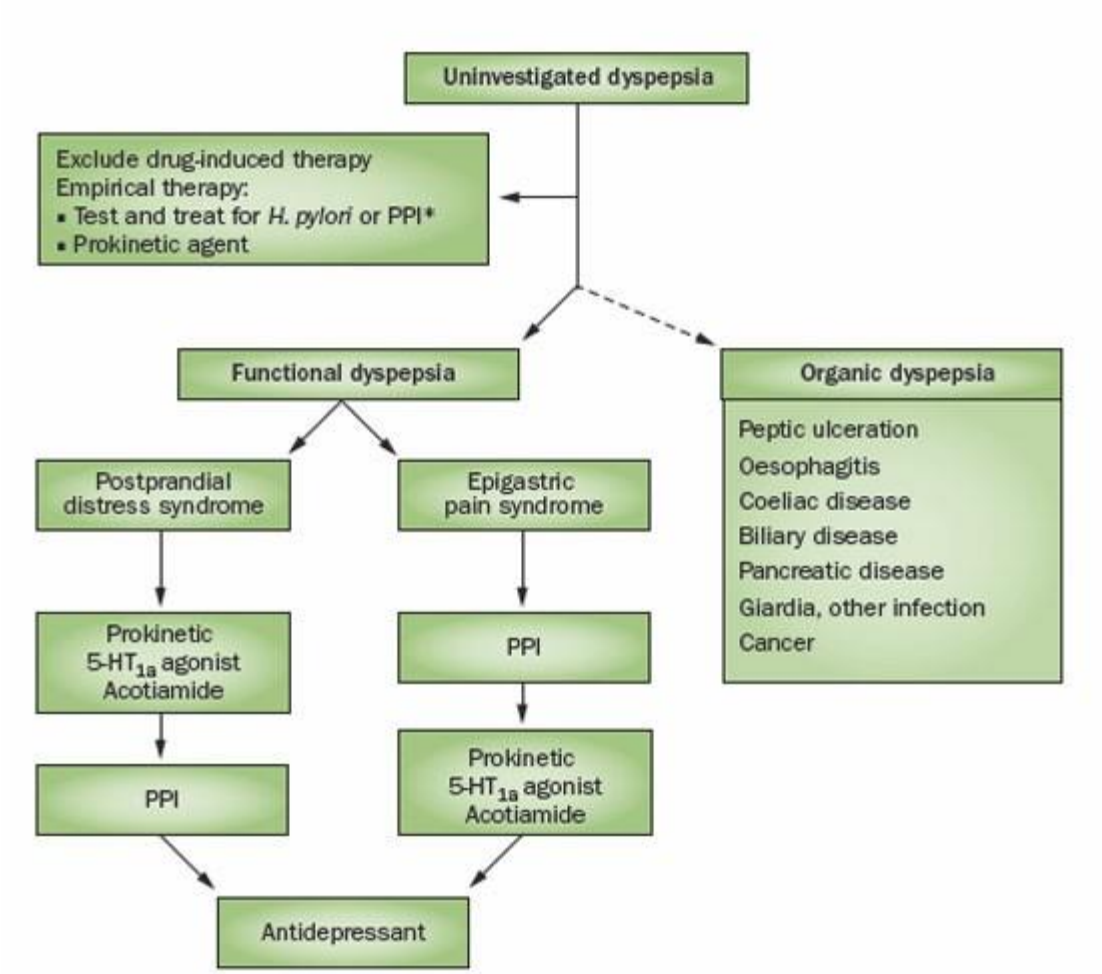
Peritonitis

By longtime, the lining of digestive system break down by stomach acids, which causes infection called peritonitis

Treatment: medications or surgery are necessary.

7 Treatment

Symptoms of dyspepsia overlapped with GERD and irritable bowel syndrome which make its management difficult, and if there is a H. pylori infection it should be treated also. Therefore, a scheme was developed to manage undiagnosed cases, as shown below[10]:



- **Pharmacological treatment :-**

In the following table there is a group of drugs used for the treatment of dyspepsia [11-13]

Functional Dyspepsia Treatment

Treatment	Efficacy
Proton pump inhibitors	Superior over placebo
H. Pylori treatment	Small but significant benefit vs. placebo
Metoclopramide	No controlled studies
Domperidone	Global improvement w/o improvement in GE
Low dose TCA	RCT showed benefit vs. placebo
SSRI	RCT showed lack of efficacy
Buspirone	Improved symptoms, ↑ fundic accommodation
Herbal therapy	Iberogast (STW 5) and Artichoke leaf extract and COLM-SST improved global symptoms vs. placebo
Psychological and behavioral	CBT and hypnotherapy showed benefit
$5HT_4$ agonists	Prucalopride for subgroup with delayed GE

- **Non pharmacological treatment:**
- **Phytotherapy :**

There is modern evidence provides the efficacy of the herbal medicine in treating the dyspepsia, in this report we show the efficacy of some of these herbal medicines.

1. **<u>Greater celandine</u>**

   origin: Chelidonium majus L.

   Family: Papaveraceae

   Part of use: Rhizome

Chelidonium majus

   Active compounds: at least 20 different alkaloids

Uses: it is found that the rhizome is antidiarrheal, carminative, and it also has analgesic properties. In addition, it has anti-spasmolytic action on smooth muscles and stimulate bile flow due to its alkaloid contents[14, 15]

2. **Licorice**

origin: Glycyrrhiza glabra L.

Licorice root

Family: Leguminosae

Part of use: Rhizome

Active compound: glycyrrhizin, also known as glycyrrhizic acid.

Uses: licorice has a brain-strengthening properties, analgesic, carminative, and scavenging properties. In addition, it has an anti-inflammatory, analgesic, antiulcer, anti-Helicobacter pylori activities, and enhancing gastric mucus secretion[16, 17]

3. **black cumin**

origin: Nigella sativa L.

Black cumin seeds

Family: Ranunculaceae

Part of plant: Seed

Active compounds: fixed oil, proteins, alkaloid, saponin and essential oil.

Uses: this plant used for inflammation, infection, and gastrointestinal problems such as flatulence, dysentery, nausea, and diarrhea. Besides that, it has an anti-inflammatory activity and affects the immune system, so it has an antibacterial activity against H. pylori. It is considered a histamine release inhibitor, and has antiulcer and gastric anti-secretory activities [18, 19].

4. **Basil**

origin: Ocimum basilicum L.

Basil leaf

Family: Lamiaceae

Part of plant: Leaf

Active compounds: methyl cinnamate (70.1%), linalool (17.5%), β-elemene (2.6%) and camphor (1.52%)

Uses: it is a carminative, strengthens stomach, nervous system, and has an antibacterial, anti-inflammatory activities, and decrease the acid and pepsin output [20, 21]

5. **Indian gooseberry**

origin: Phyllanthus emblica L.

Indian gooseberry fruit

Family: Phyllanthaceae

Part of plant: Fruit

Active compounds: ascorbic acid (vitamin C), ellagitannins, such as emblicanin A (37%), emblicanin B (33%), punigluconin (12%), and pedunculagin (14%), in addition to punicafolin, phyllanemblin, phyllanemblinin, kaempferol, ellagic acid, flavonoids, and gallic acid.

Uses: it strengthens the heart, and stomach. It has an anti-nausea properties and appetite increasing plant. In addition, it has an anti-cancerous, anti-inflammatory, antibacterial activities and has a cytoprotective acid reducing features[22, 23].

6. **Mastic tree**

origin: Pistacia lenticus Desf.

Family: Anacardiaceae

Part of plant: Oleogum Resin

Active compounds: alpha-Pinene, beta-myrcene, beta-pinene, limonene, and beta-caryophyllene

Mastic tree

Uses: it affects the gastrointestinal problems specially the digestion. In addition, it has an anti-microbial activity special H. pylori, an anti-inflammatory and scavenging properties[24, 25]

7. **Ginger**

origin: Zingiber officinale Roscoe

Ginger rhizome

Family: Zingiberaceae

Part of plant: Rhizome

Active compounds: terpenes and oleoresin "ginger oil". It also contains volatile oils approximately 1% to 3% and non-volatile pungent components oleoresin

Uses: this plant is effective for digestion problems, nausea, and bloating. In addition, it has an antioxidant, free radical scavenging, antibacterial, antispasmodic, antiulcer, and anti-inflammatory properties [26, 27].

8 Prevention

Primary Prevention of dyspepsia

Important measures should be taken to prevent the occurrence of dyspepsia such as

Long term use of certain medication such as NSAIDs (e.g. aspirin, naproxen, ibuprofen)

Reducing excessive alcohol consumption

Smoking stoppage

Avoiding using large amounts of caffeine or acidic beverages

Reducing spicy foods

Cessation of illicit drugs such as cocaine

Avoiding stress because it triggers excessive gastric acid secretion

Inculcating eating healthy habits, regular exercise, and maintaining healthy weight might facilitate in avoiding dyspepsia

Changing your diet, by avoiding certain types of drinks and foods that may cause indigestion, such as coffee; carbonated drinks; alcoholic drinks; foods that contain a lot of spicy, and acid, fatty, or greasy foods[28].

Effective measurement for primary prevention of the Helicobacter pylori infection may include [29, 30]:

Hand washing (antibacterial soaps)

Avoid contaminated food and water

Maintain proper hygiene (hand sanitizers, antiseptic washes)

You should avoid being in close contact with infected patients

The best choice for the treatment of peptic ulcer disease with MALT lymphoma is H. pylori eradication

The recommended step for the prevention of peptic ulcer is test and treat strategy in NSAID users

9 References

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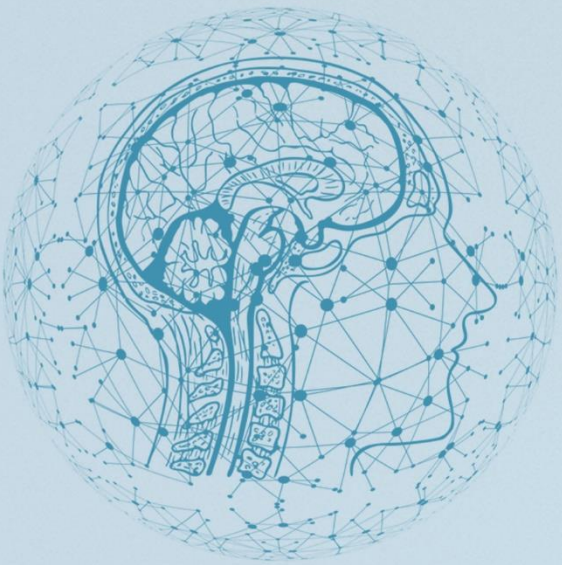
Migraine Phytotherapy



Phytotherapy
Clinical Pharmacy Level 9

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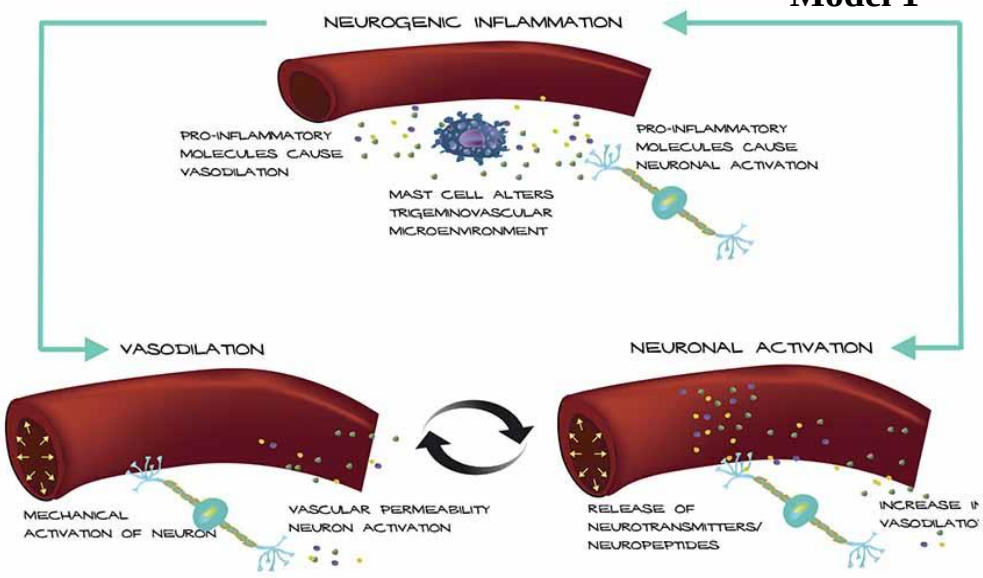
I. Introduction

What is migraine?

Afferent regulation and control are likely to be altered in migraine, with the cranium being the primary focus. According to current theories, migraines are caused by disturbances in the brain's subcortical aminergic sensory modulatory systems, as well as in the brainstem, hypothalamus, and thalamus. Although it's common for people to misunderstand migraine attacks for as severe headaches, this is not the case. A migraine can last several days if it is left untreated. Migraine can make it difficult to finish your daily tasks and even hard to getting out of bed. A migraine episode may also be preceded by warning signs for some people, known as the Aura. Auras do not, however, occur in all migraineurs. Although migraine can start at any age, it is typically diagnosed in patients in children and teenagers, 20s, or 30s. Women are diagnosed with migraines more frequently than men, and the condition often occurs in families. Different people experience migraine attacks at different frequencies. A few episodes may occur for some people each year, while many others may experience several in a single week. [1] [2]

Causes of Migraine

Model 1



Although the precise origins of migraines are yet unknown, inflammatory mediators, environmental factors, and genetics all appear to have a role. The trigeminal nerve, an important pain route, and its interactions with the brainstem could be involved. The same might be true for abnormalities in neurotransmitter levels, such as serotonin, which aids in pain regulation. [4] [5]

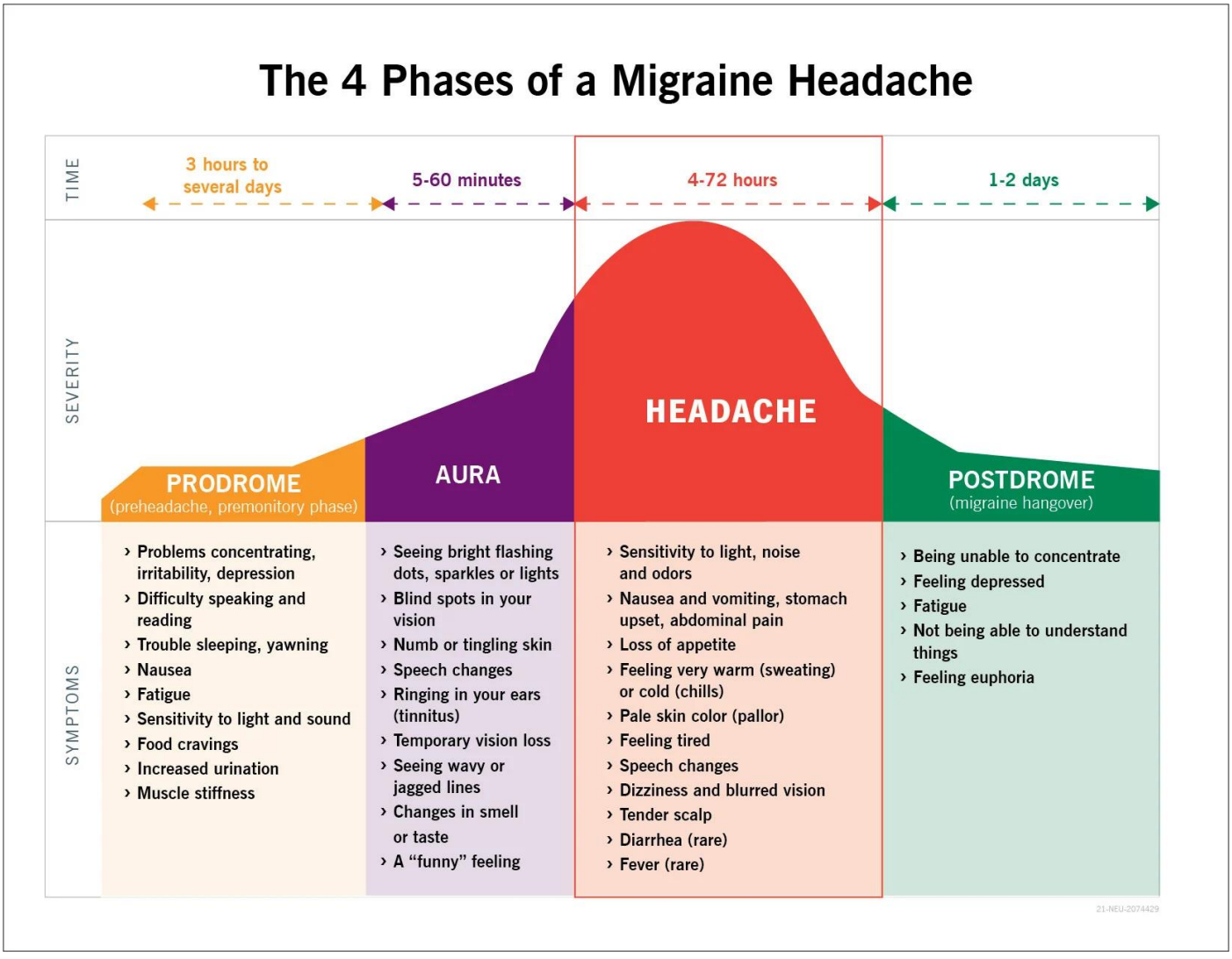
Specific nerves in your blood vessels provide pain messages to your brain causing the blood vessels and nerves to get inflamed, as explained in Model 1. By releasing inflammatory chemicals that mediate dilatation of adjacent arteries and activate the nociceptor receptors, mast cell activation and degranulation change the trigeminovascular microenvironment. Due

to increased vascular permeability, vessels mechanically trigger trigeminal neurons or release inflammatory mediators, resulting in headache pain. [3]

Migraine Phases and associated symptoms

The four stages in chronological order are the prodrome, aura, headache and postdrome. [4]

1) Prodrome: The first phase might last a few hours or even days.
2) Aura: The aura phase may last on for up to 60 minutes or only for five. Auras are uncommon, and some people even experience them together with their headaches.
3) Headache: The duration of the headache ranges from four to 72 hours. The pain is occasionally modest.
4) Postdrome: The postdrome phase lasts for one to two days. 80% of people with migraines get what is commonly referred to as a migraine "hangover."



Who is susceptible to migraines? What comes with a risk?

Although it can be challenging to predict who will experience migraines and who won't, there are some risk factors that may make you more susceptible. These risk elements consist of: [4]

- Genetics:
  Up to 80% of individuals who experience migraines have a first-degree relative who also suffers from the condition.
- Gender:
  Due to the impact of hormones, women are probably more likely to experience it.
- Tension level:
  High levels of stress trigger the release of cortisol levels which in return makes migraines happen frequently.
- Smoking.

Migraine triggers

The triggers **[Table 1]** are very subjective, so it is usually challenging to determine whether something is truly a trigger or whether what you're feeling is an early sign of a migraine attack. [6]

Table 1

Hormonal changes	Estrogen levels trigger migraine headache in women during their menstrual cycle.
Emotional triggers	Stress Anxiety Tension Shock Depression
Physical triggers	Tiredness Poor-quality sleep Poor posture Neck or shoulder tension

Dietary triggers	Missed, delayed or irregular meals Dehydration Alcohol Caffeine Chocolate and citrus fruit Foods containing tyramine (old cheese)
Environmental triggers	Bright lights Flickering screens, such as a television or computer screen Loud noises Changes in climate (humidity, very cold temperatures) Exposure to smoke, perfumes, or other odours.
Medicines	Combined contraceptive pill Hormone replacement therapy (HRT)

Migraine Diagnosis

There is no particular test to identify migraines. A general practitioner (GP) must recognise a pattern of recurrent headaches and the accompanying symptoms in order to make an accurate diagnosis. Sometimes migraines may not show up with the other symptoms, which makes them unpredictable. It may be helpful to keep a diary of your migraine attacks for a few weeks to aid in the diagnosis. Making a list of the painkillers you take and how frequently you take them along with having a note of the day that your period begins may also be beneficial for women, as keeping track of those will help your doctor in identifying potential triggers. Magnetic Resonance Imaging (MRI) and Computerized Tomography (CT) are tests to be used if your condition is unusual, complex, or unexpectedly seems extreme. [7]

II. Treatment

A. Pharmacological treatment [8-20]

Acute attack treatments

The aim is to prevent or reverse the progression of migraine attacks.

1- Triptans:

Drugs: Sumatriptan, zolmitriptan, rizatriptan, naratriptan, eletriptan, almotriptan and frovatriptan.

Mechanism of action: 5-hydroxytryptamine–1 (5-HT1) agonists.

Routes of administration: oral, nasal, SC and IM.

Precautions:

• Triptans are taken during the acute attacks only.

• The maximum dose is 2 doses daily.

• It shouldn't be used for more than 3 days weekly, as it may cause transformed migraine or medicine induced headache.

• They cannot be used by patients with cardiovascular diseases (as coronary artery disease as they are vasospasms.)

• Not used in severe or complicated migraines.

2- Ergot alkaloids:

Drugs: Ergotamine, dihydroergotamine.

Mechanism of action: Partial agonist on 5-HT2 and α-adrenergic receptors.

Routes of administration: oral, nasal spray, parenteral, sublingual, and rectal.

Precautions:

• They cannot be used by patients with cardiovascular diseases (as coronary artery disease) as they are vasospasms.

• Contraindicated in pregnancy (Category X).

• They may worsen migraine-related nausea and vomiting.

3- Analgesics:

a) NSAIDs:

Drugs: Aspirin, acetaminophen, ibuprofen, etc.

Mechanism of action: Cyclooxygenase enzyme (COX) inhibitor.

Routes of administration: Mostly used in oral form, but they are available in topical and parental forms.

Precautions:

• They cannot be used by patients with GIT, renal, CVS and hepatic problems.

• Contraindicated in 3rd trimester of pregnancy and in NSAID hypersensitivity.

• Shouldn't be used by patients with age less than 19 years old (risk of Reye's syndrome).

b) Opioids:

They shouldn't be used in the treatment of migraine.

4- Newer agents

a) Lasmiditan:

It is approved by FDA in October 2019

Mechanism of action: The mechanism is not clear, but it is suggested to be 5-HT1F receptor agonist. It reduces pain, nausea, and sensitivity to light or sound.

Routes of administration: Oral.

Precautions:

• Don't use more than one dose daily.

• It may cause sedation effect, so wait at least 8 hr before driving or operating machinery.

b) Calcitonin Gene-Related Peptide (CGRP) receptor antagonists:

Drugs: rimegepant and ubrogepant.

Mechanism of action: Blocks CGRP receptors, decrease CGRP level which is thought to be related to migraine.

Routes of administration: Oral

Precautions:

• They are potent CYP3A4 inhibitors, so be aware with other drugs that are metabolized by the same enzyme.

• Don't take a second dose of this class within 2 hr of the first one.

5- Antiemetics:

They are used in relieving migraine

Drugs: Chlorpromazine, metoclopramide, prochlorperazine and promethazine.

Precautions: Contraindicated in pregnancy.

Prophylactic therapy

The aim is to reduce the frequency of attacks and the duration of each attack and improve the quality of life.

1- Medications:

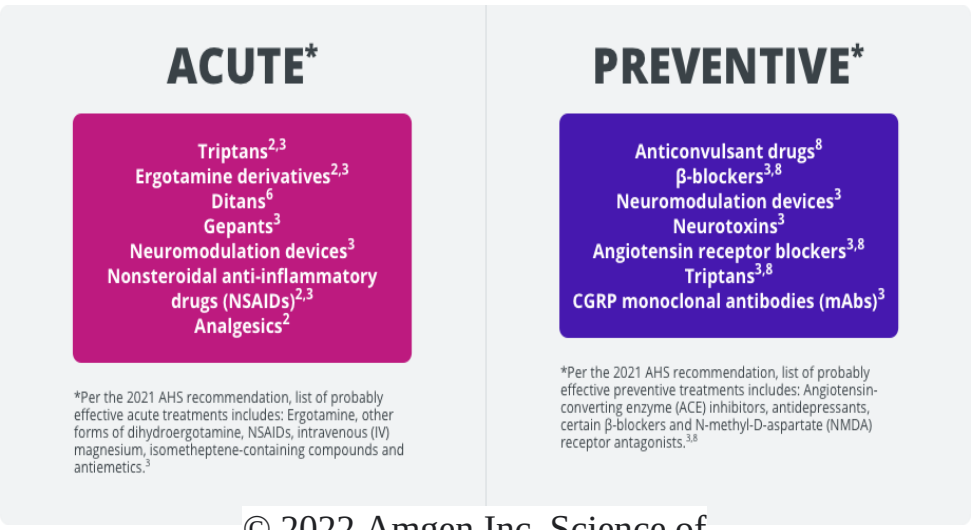
• **Antihypertensives***:* Beta blockers (e.g., Propranolol), Calcium channel blockers (e.g., verapamil), angiotensin-converting enzyme inhibitors (e.g., enalapril)

• **Anti-epileptics***:* valproate, topiramate

• **Antidepressants:** TCAs (e.g., amitriptyline) and SSRIs (e.g., Sertraline).

• **Botulinum toxin** (Botox)

• **CGRP monoclonal antibodies:** Galcanezumab, erenumab



2- Herbs:

• Lavender oil: It can be applied on the forehead or inhaling it may help in reducing the frequency of attacks.

• Peppermint oil: as lavender oil

• Ginger: It has pain-relieving and anti-emetics effects.

• Magnesium: Some studies show that it could prevent attacks.

B. Non-pharmacological treatment [8-20]

1- Devices

• *Single-pulse transcranial magnetic stimulation (sTMS):* It is a device replaced in the back of the head at the beginning if the aura helps in reducing the headache pain.

• *Neuromodulation devices:* They are devices that affects vagus and trigeminal nerves helps in preventing and relieving from attacks.

• Transcutaneous electrical nerve stimulation device.

2- Lifestyle and home remedies

• Relaxation technique: Close your eyes and relax in a dark and quiet room.

• Drinking water frequently to stay hydrated also helps.

• Good lifestyle: Sleep and wake up early at definite times and have enough hours of sleep.

• Exercise and sports: Walking, cycling and other aerobic sports help in reducing migraine attacks. Yoga and meditation can also help in relaxing.

• During attacks tying your forehead or using cool compresses help in reducing the severity of pain.

• Stay out of stress and avoid triggers

3- Alternative medicines:

• *Cognitive behavioural therapy (CBT):* Actions you can learn help in affecting your sense of pain.

• *Acupuncture*: A technique in which thin needles are inserted at definite points help in reducing the pain

C. Herbal treatment [21-59]

Herbal therapy offers a different approach than medical therapy as it focuses on preserving a healthy natural balance in the body and promoting health especially in chronic illness. It offers a complementary treatment with fewer risks and side effects and provides a more affordable option than pricey prescription drugs.

There are a lot of herbal drugs that may be considered as a good migraine headache treatment, including:

1- Feverfew

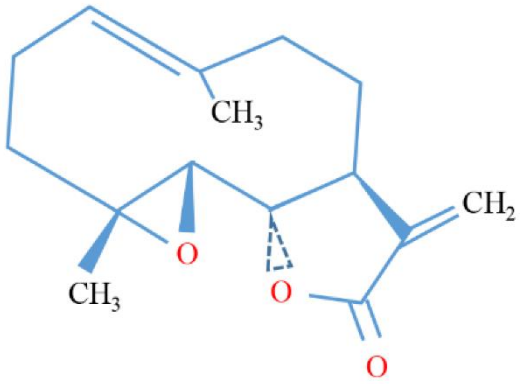
Origin: *Tanacetum parthenium L.*
Family: Asteraceae

Part used: Dried leaves and aerial parts

***Active constituents*:**
Sesquiterpene lactones, the principal one being *parthenolide*, found in the superficial leaf glands (0.2%–0.5%), but not in the stems, and comprises up to 85% of the total sesquiterpene content. Other active constituents include flavonoids, quercetin, apigenin, and some volatile oil, including camphor and camphene. The compound of interest which is responsible for alleviating migraine is ***Parthenolide***. [21]

Uses:

Feverfew is used as anti-inflammatory by inhibition of PG synthesis and histamine release which makes it useful in treating arthritis and fever. Along with that, it also has anti-vasospasm activity and anti-platelet activity through inhibition 5-HT secretion. It also has a famous migraine alleviating ability, this effect does not appear to be limited to a single mechanism but works through multiple ones. [21]



(A) Parthenolide (PN)

Evidence based medicine:

Patients using feverfew for up to 6 months of treatment reported less headaches, according to research including 8 individuals who received feverfew medication and 9 placebo-controlled patients. Before participating in the trial, patients in both groups had used feverfew as a self-medication for several years. When patients switched from feverfew to placebo during the experiment, the occurrence of headaches nearly tripled, but it stayed constant in those on feverfew ($P < 0.02$). Researchers hypothesised that feverfew would be helpful in not only classical migraine and cluster headaches but also for other types such as premenstrual, menstrual, and other migraines. Despite contradictory findings, some studies show feverfew may have a similar antimigraine effect as methysergide maleate, a medication used to treat migraines having 5-HT antagonist action. [21]

Safety profile and contraindications:

The plant's leaves have been demonstrated to have possible emmenagogue effects, thus pregnant women shouldn't take it. It is not advised for usage in infants or breastfeeding mothers. [21]

Preparation and Dosing:

Supplements containing feverfew are available in capsules, tablet, and liquid extract formulations, and can be obtained fresh, freeze-dried, or dried. Supplements containing feverfew should be standardised to have parthenolide levels of at least 0.2%. [21]

Adult dosage each day : Must have 100–300 mg up to four times every day.

2- Coriander

Origin: *Coriandrum sativum L.*

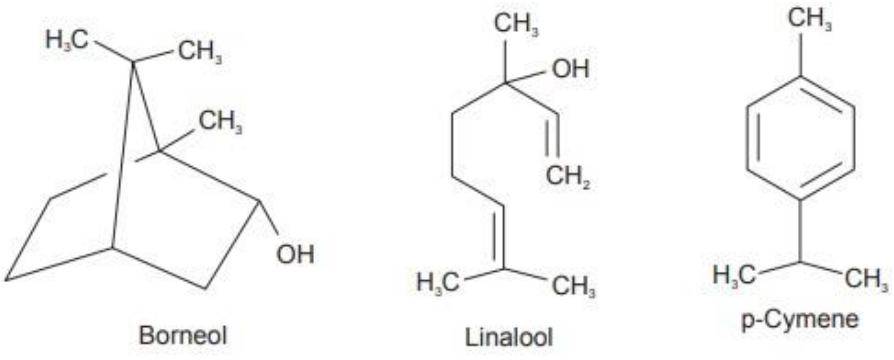
Family: Umbelliferous

Part used: Dried seeds and leaves

Active constituents:

Volatile oil as a main component, *linalool (Coriandrol)*. Coriander has other chemical ingredients such as fatty oils and furanocoumarins. [22] [24]

Uses:



Gastric secretion is stimulated by coriander essential oil. It has benefits as a carminative, eupeptic, estrogenic, anxiolytic, and spasmolytic. It also has antibacterial and antifungal effects. [22] [24]

Due to coriander properties, it has an anti-migraine effect. [23]

Evidence based medicine:

Several placebo-controlled trials have been documented about Coriander syrup's effect on migraine and it was found to control it. Additionally, results of a study on mice illustrated that linalool is effective in chronic pain, via the inhibition of inflammatory mediators. Also, linalool is one of the components of Lamiaceae family and various investigations have confirmed the analgesic and anti-inflammatory effects of several species, belonging to this family. [23]

Contraindications and safety profile:

Coriander fruits at a dose of 750 mg/kg caused no mortality in rats, and LD50 for the oil was found 4.13 g/kg. However, high doses of coriander fruits (500 mg/kg) inhibited implantation in female rats significantly and had a small abortifacient (but no teratogenic) effect on the rats. [22]

It should not be used during pregnancy, lactation, and hyper-estrogenism. The pure essential oil is irritating. High oral doses may cause convulsions. [24]

Preparation and Dosing:

It´s administered in powder form and other pharmaceutical preparations for internal use.

Infusion: A freshly prepared cup between meals can be considered as a daily dose. [24]

3- Valerian

Origin: *Valeriana officinalis L.*

Family: Caprifoliaceae

Part used: Dried root and rhizome

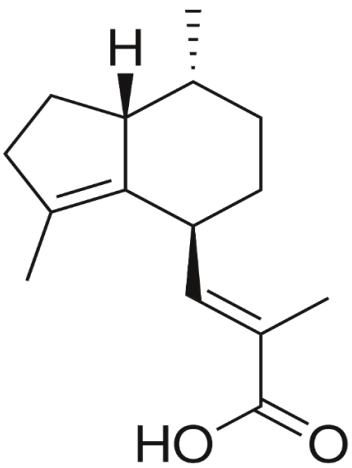
Active constituents:

The main active constituents are alkaloids, organic acids, and terpenes.

Terpenes: chemically characterized as monoterpenes and sesquiterpenes. Most considerable are valeric, isovaleric, valerenic, and isovalerenic. Some of the oil's constituents may have sedative effects. The chemicals that give valerian its distinctive odour are isovaleric acid and bornyl isovalerate. [25]

Uses:

Valerian is a gentle sedative that promotes sleep and is frequently used as a milder substitute or potential replacement for stronger synthetic sedatives like benzodiazepines, in the treatment of nervous states and anxiety-induced sleep disturbances it also treats tension-type headache and migraine as will be discussed below. [25]



Valerianic Acid

Evidence-based medicine:

There are some other studies about the analgesic effect of valerian on migraine. The effectiveness of V. officinalis capsules in people with migraine attacks who had previously received sodium valproate treatment was examined in a randomised clinical trial study; the findings showed that valerian capsule significantly decreased the frequency, duration, and intensity of migraine attacks. [26]

Mechanism of action:

The volatile oil, monoterpene, valepotriates, and sesquiterpene components of valerian are thought to be responsible for the pharmacological actions. Some of these components were believed to have direct effects on the brain, whereas valerenic acid protects the γ-amino butyric acid (GABA) neurotransmitter from being destroyed by enzymes, which eventually causes sleepiness. Stress is one of the major risk factors for tension-type headaches, thus lowering stress may be a possible explanation for the beneficial effects of valerian. [26]

Contraindications and precautions:

Women who are pregnant or nursing and children younger than 3 years old should not take valerian because the possible risks to these groups have not been evaluated. Individuals taking valerian should be aware of the theoretical possibility of additive sedative effects from alcohol or sedative drugs, such as barbiturates and benzodiazepines. [28]

Safety profile:

Clinical research suggests that valerian is a moderate tranquillizer that is generally safe to use instead of benzodiazepines. [25] Valepotriates, which are a component of valerian but are not necessarily present in commercial preparations, had cytotoxic activity in vitro but were not carcinogenic in animal studies. [28]

Formulations:

Sesquiterpenes are regarded to be in charge of the pharmacological impact of Valerian herb. According to one study, tinctures and teas included the least quantity of valerenic acids, whereas powder capsules had the maximum concentration. [29]

Dosages of Valerian:

For headache, a capsule contained 530 mg of dried valerian root extract was reported to be efficient. [26] Doses also vary depending on the purpose of treatment, though a dose range between 600-900 mg was found to be optimal in efficacy with low toxicity profile. [28]

4- Butterbur

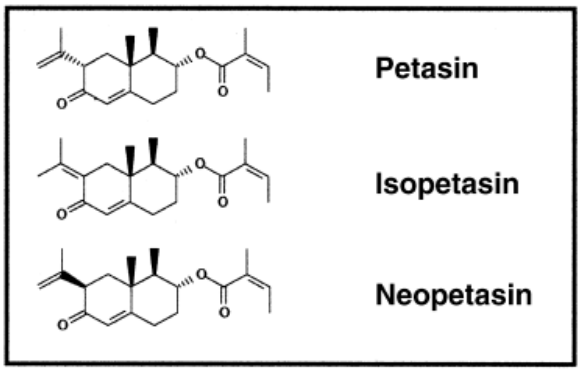
Origin: *Petasites hybridus L.*

Family: Asteraceae

Parts used: Entire Herb

Active Constituents:

Sesquiterpenes consisting primarily of petasin and isopetasin.[32]



Uses:

Butterbur is used for lower back pain, digestive system spasms, and urinary tract spasms because of its antispasmodic properties. Asthma and whooping cough have also been treated with Butterbur ingredients. In a clinical investigation, it was discovered that the antihistamine cetirizine and a leaf extract (standardised to petasin concentration) were equally effective for treating allergic rhinitis. Butterbur also has significant anti-migraine effect. [32]

Migraine Treatment Mechanism:

Herb's sesquiterpenes (Petasin and Isopetasin), which have been found to exhibit anti-inflammatory effects through the inhibition of COX-2, have led to decreased leukotriene synthesis and prostaglandin E2 release, and specifically Petasites inhibit the opening of L-type voltage-gated calcium channels, decreasing vasoconstriction of vessels and excitation of neurons. [33]

Evidence-based medicine:

The effectiveness of the dried butterbur extract in the treatment of migraines was examined in two randomised, placebo-controlled, double-blind clinical studies. 60 patients diagnosed with migraine were randomly assigned to receive either 50 mg of the extract or a placebo in the first experiment. The number of migraine attacks significantly decreased in the butterbur extract group compared to the placebo group beginning in the fourth week of therapy. In addition, the butterbur group had fewer migraine days than the placebo group. After the 12-week study period, there were no adverse events recorded. [32]

Safety profile:

The pyrrolizidine alkaloids (PAs) found in butterbur leaf and rhizome are potentially hepatotoxic and carcinogenic components. It is critical that healthcare practitioners should suggest PA-free butterbur products. All limits refer to PAs with the 1,2 necine structure, including their N-oxides. [32]

Contraindications and side effects:

The PA-free extract infrequently causes side effects, which often involve moderate digestive upset and skin rashes. One instance of cholestatic hepatitis was identified as a hypersensitive response, with butterbur being the likely causative agent. Due to a lack of safety research, butterbur shouldn't be taken by people who are pregnant, breastfeeding, or who have had hepatitis or other liver conditions. Butterbur rhizome extract does not appear to interact with any medications. [32]

Preparation and Dosing:

Migraine prevention: A pyrrolizidine-free butterbur rhizome extract with 7.5 mg of petasin and isopetasin per 50 mg tablet (Petadolex), dosed at 50–75 mg twice daily for up to 4 months, has been evaluated for usage as a preventative treatment for migraines. [35]

5- Willow

Genus: Salix

Family: Salicaceae

Part used: Bark

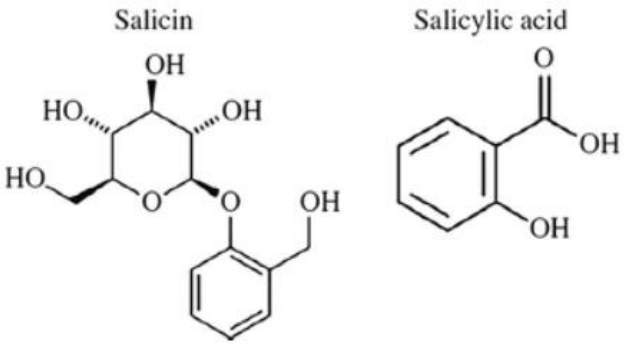
Active constituents:

Willow bark contains flavonoids, glycosides (phenolic and non-phenolic glycosides), procyanidins, organic acids and their derivatives, simple phenolics, sterols and terpenes, lignans. Moreover, Glycosides are major secondary metabolites in Salicaceae. Phenolic glycosides represent up to 30% of dry plant mass. They are classified into two main classes: Salicin derived glycosides (salicinoids) and other phenolic glycosides. [36]

Uses:

Willow bark acts a lot like aspirin. Aspirin is used to treat mild to moderate pain, including migraine headache, inflammatory disorders such as rheumatoid arthritis, and, at low dosages, cardiovascular disease. [36]

Willow is used for pain, including headache, muscle or joint pain, menstrual cramps, rheumatoid arthritis (RA), osteoarthritis, and gout. Salicin derived glycosides work in a similar way as aspirin (derived from salicylic acid). They exert analgesic, anti-inflammatory, antioxidant, anticancer, cytotoxic, antidiabetic, antimicrobial, anti-obesity, neuroprotective and hepatoprotective activities. [38]



Mechanism of action:

Salicin is a major pharmacologically active metabolite in salix and hydrolyses in the gastrointestinal tract forming salicyl alcohol, in which it is oxidized into salicylic acid, the

active drug which inhibits cyclooxygenases pathways to give the analgesic effect in migraine treatment. [37]

Evidence-based Medicine: [37]

There are many randomized double-blind studies that confirm the efficacy of aspirin in this regard compared to placebo.

Aspirin 900 or 1000 mg versus placebo in headache relief reported for one hour

Data was provided by four trials (1288 individuals) comparing aspirin 900 mg or 1000 mg versus placebo.

• 33% of individuals reported headache reduction after one hour of taking aspirin 900 mg or 1000 mg.

• The proportion of participants experiencing headache relief at one hour with placebo was 15%

Aspirin 1000 mg versus placebo In Sustained headache relief at 24 hours against Placebo

This result was based on data from three research (1142 individuals).

• 39% of individuals had 24-hour sustained improvement from aspirin 1000 mg.

• With placebo, 24% of subjects had 24-hour sustained alleviation.

The conclusion of the studies was that Aspirin 900 mg or 1000 mg is an effective treatment for some individuals with acute migraine headaches.

Contraindications and Adverse Effects:

It is a strong gastrointestinal irritant that can induce pain, ulcers, and bleeding. It may also cause tinnitus at high doses, and it is no longer used in children and adolescents, in whom it may cause Reye's syndrome (swelling of the brain that may lead to coma and death). The drug interaction profile of aspirin is full of problems. It's not recommended for pregnant and breastfeeding women. [37]

Precautions

Willow bark safety concerns are comparable to those presented by salicylate treatment.

Willow bark can produce stomach upset, nausea, vomiting, and bloody stool. In individuals who are also taking antiplatelet drugs or other salicylate-containing products, it should be taken with caution. Pregnant women are advised to avoid it. Those with sensitivity towards salicylates should also avoid it. [39]

Preparation and Dosing:

Willow bark should be dosed according to the salicin content in the supplement: salicin, 120–240 mg orally in two to three divided doses daily. [39]

6- Rosemary

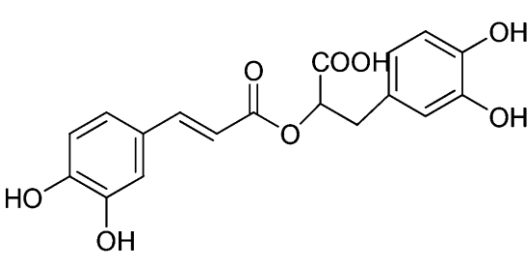
Origin: *Rosmarinus officinalis*

Family: Lamiaceae

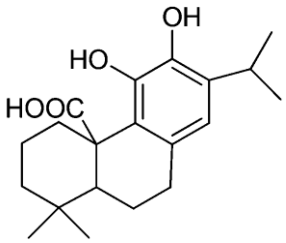
Part Used: Leaves

Active constituents:

Triterpenes, phenolic diterpenes, and phenolic acids, such as rosmarinic acid, carnosic acid, rosmanol, carnosol, ursolic acid, and betulinic acid, are the most prominent active ingredients. Among the phenolic compounds mentioned, **rosmarinic acid** and **carnosic acid** have the most therapeutic benefits. [42]



Rosmarinic acid



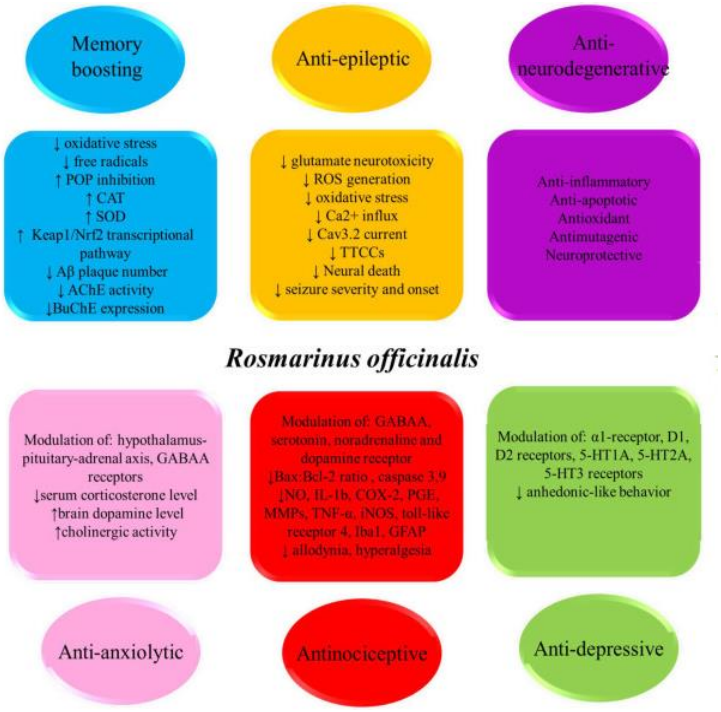
Carnosic acid

Uses:

Mild analgesic, antispasmodic, bacterial, anti-inflammatory, antioxidant, anti-tumorigenic, and antinociceptive are some of rosemary herb known uses. Numerous research has focused on the neuropharmacological aspects of rosemary. Along with having potent antiepileptic, anti-depressive, and neuroprotective effects, Rosemary exhibits notable clinical benefits on pain, anxiety, memory, learning, mood, and sleep. [40] [41]

Mechanism of action:

Axon and myelin derangement, edema, and inflammatory infiltration were all inhibited by rosemary extract, terpenoid-enriched. The collected information supported the historic usage of rosemary as a potent painkiller and anti-inflammatory. These findings further imply that rosmarinic acid may hold promise for the treatment of neurological conditions characterized by neuro-inflammation and neuropathic pain. The information could indicate that rosmarinic acid may be effective against inflammatory and oxidative markers such as IL-1b, PGE-2, NO, COX-2, and MMP2. [40]



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doi: 10.22038/ijbms.2020.45269.10541

Contraindications:

Additionally, the FDA in America has classified rosemary as "generally recognised as safe," or GRAS. In mice, rosmarinic acid was found to have an extremely low LD50 of 561 mg/kg. Therefore, no contraindications have been found. [40]

Pregnancy/Lactation:

Rosemary is best avoided by pregnant women due to its potential emmenagogic and abortifacient effects. [41]

Adverse Reactions:

There have been some adverse reactions of dermatitis, allergies, and photosensitivity to rosemary extracts or oil. Although there aren't many case reports of rosemary-related seizures, there is a chance for toxicity, presumably because of the high camphor level of rosemary oil. [41]

Dosing:

Different rosemary formulations have been utilised for numerous reasons. In a clinical

research, dried rosemary leaf powder was administered orally at low doses (750 mg) to help older individuals with their memory recall, but greater doses (6 g) had the opposite effect. [41]

7- Lavender

Origin: *Lavandula angustifolia*

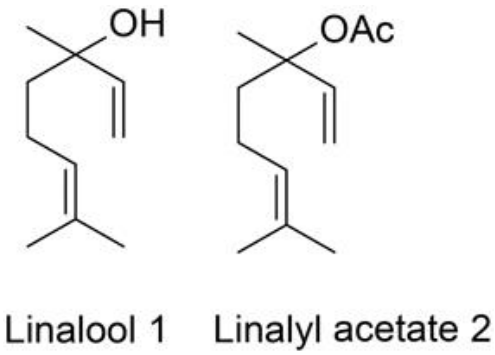
Family: Lamiaceae

Part used: Flower

Active constituents:

In addition to being grown primarily for its essential oils (Lanalool and Linalyl acetate), lavender also features bioactive substances, including polyphenols, coumarins, triterpenes, sterols, and tannins. [42]

Uses:



Linalool 1 Linalyl acetate 2

Due to their capacity to chelate metal ions (such as Fe2+ and Cu2+) and suppress the activity of pro-oxidative enzymes, polyphenols have antioxidant action [42].

With a long history of therapeutic usage, lavender is thought to have soothing, antidepressant, anxiolytic, anticonvulsant, and antidepressant effects. Some doctors from the Middle Ages, like Ebn-e-Sina and Razi, recommended lavender as a cure for epilepsy and migraines. Lavender is also thought to be helpful in the treatment of pain and tremor [43].

Mechanism of Action:

The findings indicate that the glutamate NMDA-receptor is a safe target for migraine therapy since lavender essential oil and its main components have a dose-dependent affinity for

NMDA receptors. Lavender also has the ability to inhibit the serotonin transporter (SERT), which makes it an antidepressant. [47]

Evidence-based medicine:

After topical application and massage, linalyl and linalyl acetate are quickly absorbed via the skin and are considered to be able to calm the central nervous system. [43].

There were two groups of 47 individuals with a confirmed diagnosis of migraine headaches: cases and controls. Cases breathed liquid paraffin for the same amount of time that the control group did while inhaling lavender essential oil for 15 minutes. For a total of two hours, patients were asked to note the intensity of their headaches and any accompanying symptoms at 30-minute intervals. Results: According to the Visual Analogue Scale score, the mean reduction in headache intensity in the patients was 3.6 ± 2.8. In controls, the decrease was 1.6 ± 1.6. With $p < 0.0001$, this distinction between the controls and cases was statistically significant. Conclusion: According to the results of this study, inhaling lavender essential oil may be a reliable and secure method of treating migraine headaches. [44]

Side effects:

Common side effects of lavender may include: [45]

- constipation
- headache
- increased appetite
- skin irritation upon topical use

Contraindications and Adverse Drug Reactions:

There have been some reports of negative outcomes following lavender application. [43]

- In three boys aged between 7 and 10 years, gynecomastia was associated with topical product use.
- Use with caution or avoid in individuals known to have a lavender allergy.
- Unfavourable gastrointestinal effects, including nausea and dyspepsia.

Precautions:

Due to the emmenagogue effects, Lavender consumption should be avoided during pregnancy and breast-feeding. [43]

Dosing: [46]

Internal Use:

Lavender tea: 1 cup PO qD-TID; 1 - 2 tsp whole herb / 8 oz boiling water

External Use:

Inhalation: 2-3 cups boiling water with dried flowers

8- Ginger

Origin: *Zingiber officinale*

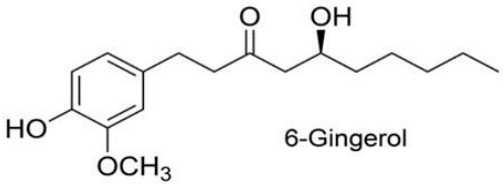
Family: Zingiberaceae

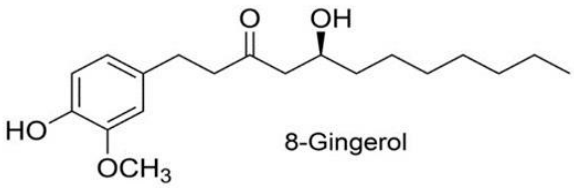
Part Used: roots and rhizomes

Active constituents:

The oleoresin from the rhizomes of ginger includes [6]-gingerol, which is the main pungent component and is thought to have a variety of notable pharmacological and physiological effects. [48]

Uses:





The efficacy of ginger as an antioxidant, anti-inflammatory agent, anti-nausea, and anti-cancer agent is proven by studies. Research findings confirm the many reports of ginger's potency as an antinausea agent and as a potential colon cancer preventive substance by showing that ginger and its contents accumulate in the gastrointestinal system. Moreover, Ginger is most frequently used to treat pregnancy-related nausea and vomiting. Additionally, ginger seems to lower cholesterol and enhance lipid metabolism, lowering the risk of diabetes and cardiovascular disease. [48]

Since inflammatory mediators are the primary cause of migraine, ginger has more recently been researched in the context of migraine in the field of neuropsychiatry. [49]

Mechanism of Action:

Ginger is thought to have anti-inflammatory properties through inhibiting COX-2, which thus prevents the creation of prostaglandins and leukotrienes. Others have demonstrated that gingerols strongly block the leukotriene production of enzyme arachidonate 5-lipoxygenase. (8) but not (6) -gingerol has been demonstrated to reduce the expression of the enzyme cyclooxygenase-2 (COX-2), which is activated during inflammation to enhance prostaglandin production. [48]

Evidence-based medicine:

In two studies that compared ginger's therapeutic efficacy to placebo, it was found that ginger increased the number of patients who reported being pain-free. The risk of nausea and vomiting brought on by migraines was reduced by half when compared to placebo, and the risk of adverse events was not changed. [49] Overall, ginger medication in migraine is linked to significantly better pain relief compared to the control group. Patients with migraines who are being treated with ginger reported pain relief after starting treatment. [50]

Contraindications and Adverse Drug Reactions:

Researchers warn that higher amounts, such those found in supplements, may raise the risk of bleeding. People using anticoagulant treatment (blood thinners including warfarin, aspirin, and others) may need to be cautious. Researchers are examining whether or not eating a lot of ginger might affect insulin and lower blood sugar. Patients with diabetes should be cautious while using ginger supplements until more information is available. [51]

Dosing:

A typical dose is a 550 mg capsule at the first sign of a headache. This dose may be repeated once or twice. [52]

9- Chamomile

Origin: German chamomile (*Matricaria recutita*)

Family: Asteraceae /Compositae

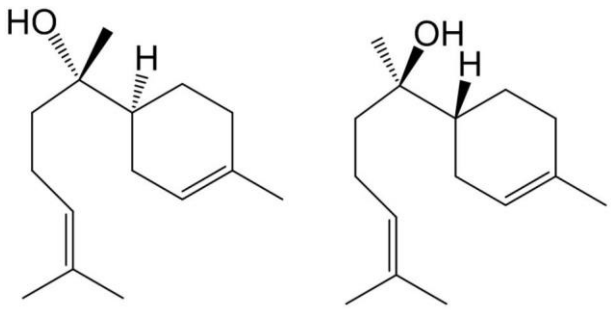
Part Used: Flower

Active constituents:

Terpenoids and flavonoids included in chamomile essential oils contribute to its pharmacological characters. The terpenoids α-bisabolol and its oxide azulenes, including chamazulene and acetylene derivatives, are the main ingredients of the essential oil derived from German chamomile flowers. [53]

Uses:

The high alpha-bisabolol content of chamomile oil makes it an effective treatment against a variety of human diseases, including inflammation, muscle spasms, menstrual irregularities, insomnia, gastrointestinal issues, rheumatic pain, and haemorrhoid. [53]



(-)-α-bisabolol (+)-α-bisabolol

Mechanism of action:

Due to the following qualities, it potentially has migraine pain relieving effects: Chamomile flavonoids, which have a potent inhibitory effect on endogenous prostaglandin E2 (PGE2) levels and can act as a selective COX-2 inhibitor; chamazulene and apigenin result in a decrease of NO release and synthesis; chamomile polyphenols reduce the inflammation in neurovascular units (NVU) at the site of migraine pain; the above modes of action lead to the hypothesis that chamomile oil is a new treatment for migraine relief. [54]

Contraindications and Adverse Drug Reactions:

It has been demonstrated to cause vomiting when consumed in the form of a tea that's been greatly concentrated. Additionally, chamomile may interact with anticoagulant, antiplatelet,

and sedative medications like benzodiazepines as well as other medications. Cytochrome P-450 may be inhibited by chamomile. Therefore, when consuming chamomile products, individuals who are taking other medications that are metabolised by the enzyme system should take caution. [55]

Pregnancy:

After receiving bisabolol 1 mL/kg over an extended period of time, rats and rabbits showed no teratogenic or developmental problems. [56]

Dosing:

Topical creams and oils have been used as different chamomile preparations.
The average oral dosage of chamomile when consumed as tea is up to 15 g/day. [56]

10- Peppermint

Origin: *Mentha piperita*
Family: Lamiaceae
Part Used: Herb

Active constituents:

The volatile oil produced by peppermint, which ranges from 0.1% to 1%, is mostly made up of menthol (29% to 48%), menthone (18% to 33%), and menthyl acetate. [59]

Uses

According to recent studies, enteric-coated peppermint oil may be useful in treating some irritable bowel diseases. Peppermint oil administered through enema has shown some minor efficacy in treating colonic spasm due to its soothing effects on smooth muscle. Peppermint oil had a substantial analgesic effect and decreased

headache sensitivity. The treatment of tension headaches may be successful when peppermint oil is applied topically. [58]

Specifically, low menthol concentrations applied topically produce a cooling feeling, but high menthol concentrations produce local anaesthesia and itching. [59]

Mechanism of Action

Menthol doses have a direct cooling action on the "cold receptor" known as transient receptor potential melastatin type 8 (TRPM8), receptors that perceive pain. Transient receptor potential ankyrin type 1 (TRPA1) has been demonstrated to have pain sensation effects at greater menthol concentrations. According to in vitro findings, menthol treatment reduced nicotine-induced activation of TRPA1 in cell cultures. [59]

Evidence-based medicine:

Two studies have demonstrated that peppermint oil used topically is useful in easing tension headache symptoms. Different topical herbal medicines were tested on 32 participants in one RCT. 15 Patients who applied a peppermint and ethanol combination saw a substantial analgesic effect compared to those who got a placebo. A 10% peppermint oil formulation significantly decreased headache severity after 15 minutes, according to a second RCT that examined the effects of topical peppermint oil and acetaminophen on 164 headaches in 41 individuals. [57]

Contraindications and Adverse Drug Reactions:

Allergies, heartburn, perianal burning, blurry vision, nausea, and vomiting are frequent. Use caution especially upon those who are using calcium channel blockers, antipsychotics, or statins. [57]

Dosage [57]

Adults: 0.2 to 0.4 mL of oil three times daily in enteric-coated capsules	Children older than eight years: 0.1 to 0.2 mL three times daily

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https://pubmed.ncbi.nlm.nih.gov/34851560/#:~:text=Ginger%20has%20been%20found%20to,the%20prevention%20of%20migraine%20episodes.

50- Liyan Chenab; Zhiyou Cai
The efficacy of ginger for the treatment of migraine: A meta-analysis of randomized controlled studies
The American Journal of Emergency Medicine
URL: https://doi.org/10.1016/j.ajem.2020.11.030

51- https://www.hopkinsmedicine.org/health/wellness-and-prevention/ginger-benefits

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Chamomile: A herbal medicine of the past with bright future
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54- Arman Zargaran, Afshin Borhani-Haghighi , Pouya Faridi , Saeid Daneshamouz, Gholamreza Kordafshari , Abdolali Mohagheghzadeh
Potential effect and mechanism of action of topical chamomile (Matricaria chammomila L.) oil on migraine headache: A medical hypothesis
DOI: 10.1016/j.mehy.2014.08.023
URL: https://pubmed.ncbi.nlm.nih.gov/25238714/

55- Adrienne Juarascio, ... Nalaka S. Gooneratne
Alternative Therapeutics for Sleep Disorders
Therapy in Sleep Medicine, 2012

56- https://www.drugs.com/npp/chamomile.html#fandc-np5081.b31

57- BENJAMIN KLIGLER, SAPNA CHAUDHARY
Peppermint Oil
Am Fam Physician. 2007; PMID: 17427617
URL:
https://pubmed.ncbi.nlm.nih.gov/17427617/#:~:text=Topical%20application%20of%20peppermint%20oil,in%20patients%20undergoing%20barium%20enemas

58- H Göbel , G Schmidt, D Soyka
Effect of peppermint and eucalyptus oil preparations on neurophysiological and experimental algesimetric headache parameters

DOI: 10.1046/j.1468-2982.1994.014003228.x
URL: https://pubmed.ncbi.nlm.nih.gov/7954745/
59- https://www.drugs.com/npp/peppermint.html

Report on

" Rheumatoid Arthritis "

Under Supervision of

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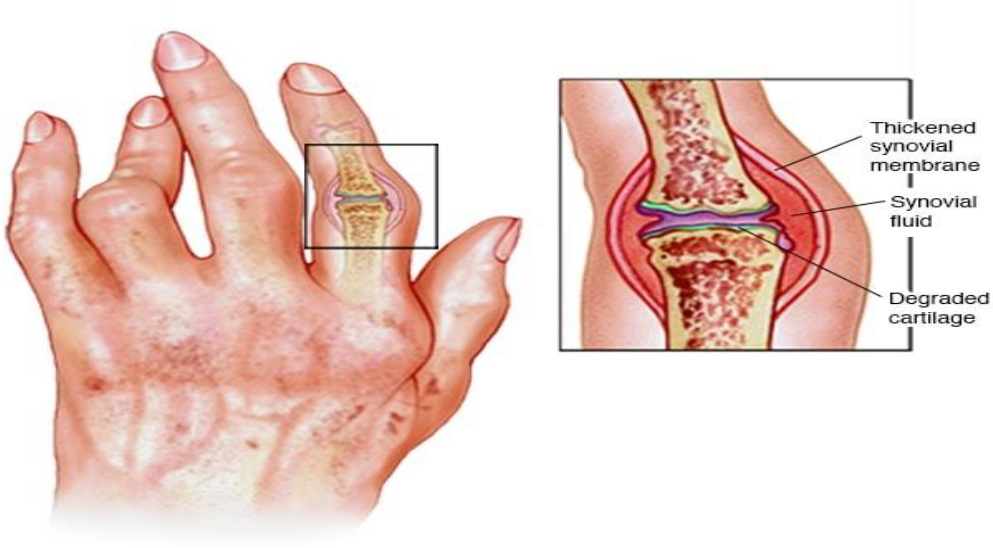
Clinical Pharmacy (Class No.9)

Contents

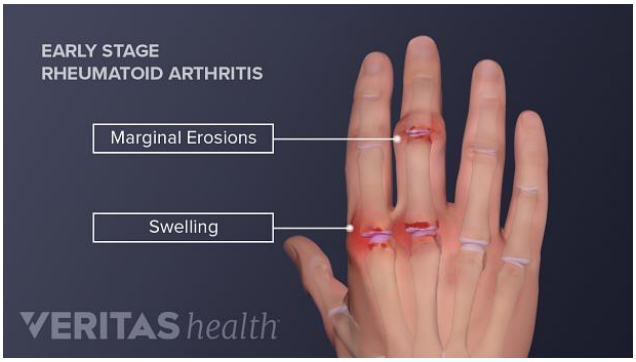


1 - Introduction

A chronic inflammatory condition, Rheumatoid arthritis will hurt quite simply your joints. Skin, eyes, lungs, heart, and blood vessels ar simply a couple of the body systems that the ill health may hurt in some individuals19. Rheumatoid arthritis is associate reaction ill health that develops once your system accidentally targets the tissues in your own body. Rheumatoid arthritis damages the liner of your joints, inflicting a painful swelling that will eventually result in bone erosion and joint deformity in distinction to osteoarthritis' wear-and-tear destruction. a pair of rheumy arthritis-related inflammation is what causes hurt to different bodily elements also. Extreme cases of Rheumatoid arthritis will still end in physical impairments, despite the actual fact that new drug sorts have considerably improved treatment prospects.[1]

[1](Reference): **Lee JE, Kim IJ, Cho MS, Lee J. A Case of Rheumatoid Vasculitis Involving Hepatic Artery in Early Rheumatoid Arthritis. J Korean Med Sci. 2017 Jul;32(7):1207–10.**

2- Symptoms



Symptoms of rheumatoid arthritis include:

Swelling, heated, and tender joints. Sometimes worst within the mornings and when inactivity, joint stiffness, fatigue, fever, and appetence loss Smaller joints, particularly people who connect your fingers and toes to your hands and feet, ar generally the primary to be full of early rheumy arthritis4. Because the ill health worsens, the wrists, knees, ankles, elbows, hips, and shoulders ofttimes begin to exhibit symptoms. The bulk of the time, a similar joints on each side of your body expertise symptoms5. Rheumatoid arthritis affects the joints in regarding four-hundredth of patients, though different signs and symptoms also can occur. Skin, eyes, lungs, heart, kidneys, and secretion glands are among the organs that might be wedged. -Bone marrow -Nerve tissue Blut vessels sixteen the severity and repetition of Rheumatoid arthritis signs and symptoms will vary. Times of relative remission, throughout that the swelling and pain subside or get away, alternate with periods of skyrocketing sickness activity, or flares. Rheumatoid arthritis will cause joints to distort and move out of position over time.[2]

---

[2]**(Reference):** McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011 Dec;365(23):2205–19.

Chaudhari K, Rizvi S, Syed BA. Rheumatoid arthritis: current and future trends. Nat Rev Drug Discov. 2016 May;15(5):305–6.

3- Causes

A reaction condition is Rheumatoid arthritis. Your system usually aids in defensive your body against ill health and infection. Your system targets healthy joint tissue if you have got Rheumatoid arthritis to boot, it will result in health problems along with your nerves, eyes, skin, heart, and lungs. Though a hereditary element is probably going, doctors do not know what triggers the start of this method. Though your genes do not directly cause Rheumatoid arthritis, they'll increase your status to the environmental conditions, like exposure to specific viruses and microorganism that will do so.

4- Risk factors

Factors that may increase your risk of rheumatoid arthritis include:

Your sex is one factor that could make you more likely to develop rheumatoid arthritis. In comparison to men, women are more likely to acquire rheumatoid arthritis.

• Age. Although rheumatoid arthritis can strike at any age, it often develops in middle age.

• Ancestral history. You may be more susceptible to developing rheumatoid arthritis if a family member does.

• Smoking. Smoking raises your chance of getting rheumatoid arthritis, especially if you are genetically predisposed to the condition. Additionally, smoking seems to be linked to a worsening of illness symptoms.

• Extra weight Overweight people seem to have a slightly increased risk of rheumatoid arthritis.[3]

5-Complications

Rheumatoid arthritis increases your risk of developing:

• Osteoporosis. Osteoporosis is a condition that weakens your bones and makes them more prone to fracture. Rheumatoid arthritis itself, as well as several medications used to treat rheumatoid arthritis, can raise your risk of developing it.

• Nodules from arthritis. The elbows and other pressure areas are where these hard tissue lumps most frequently occur. However, the heart and lungs are just two places in the body where these nodules can develop.

• Dry mouth and eyes. Rheumatoid arthritis patients are far more prone to develop Sjogren's syndrome, a condition that causes the amount of moisture in the mouth and eyes to decrease.

• Infections. Both the disease itself and several treatments for rheumatoid arthritis can weaken the immune system, which makes infections more common. Get vaccinated to protect yourself from infections like influenza, pneumonia, shingles and COVID-19.

[3]**(Reference):** McGonagle D, Hermann KG, Tan AL. Differentiation between osteoarthritis and psoriatic arthritis: implications for pathogenesis and treatment in the biologic therapy era. Rheumatology (Oxford). 2015 Jan;54(1):29–38.

Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. Nat Rev Dis Primers. 2018 Feb;4:18001.

• An abnormally composed body. Even in those with a normal body mass index, the ratio of fat to lean mass is frequently higher in those with rheumatoid arthritis (BMI).

• Carpal tunnel disorder. If you have wrist rheumatoid arthritis, the swelling may compress the nerve that supplies the majority of your hand and fingers. Heart issues. You are more likely to develop clogged and hardened arteries as well as inflammation of the sac that surrounds your heart if you have rheumatoid arthritis.

• Lung conditions. Rheumatoid arthritis patients are more likely to experience lung tissue inflammation and scarring, which can cause gradual shortness of breath.

• Lymphoma. The risk of lymphoma, a class of blood malignancies that arise in the lymphatic system, is increased by rheumatoid arthritis.[4]

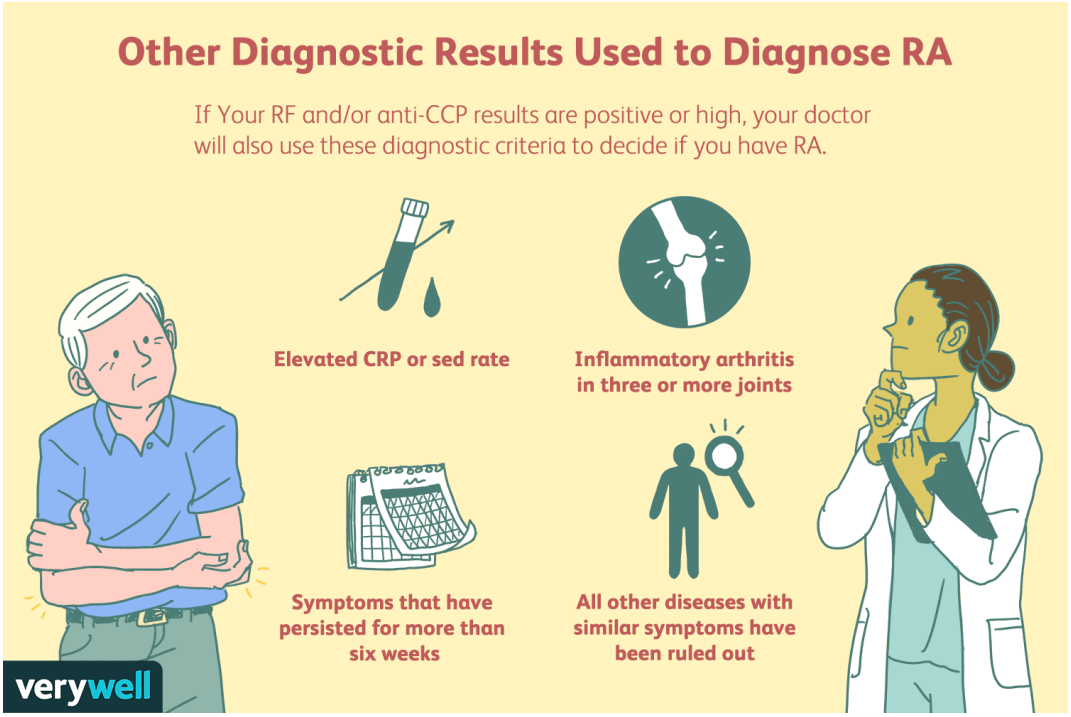
6-Diagnose

Early signs and symptoms of rheumatoid arthritis might be confusing because they are similar to those of many other diseases. The diagnosis cannot be verified by a single physical examination or blood test. Your doctor will examine your joints during the physical to look for edoema, redness, and warmth. Your reflexes and physical strength may also be tested.

[4] **(Reference):** Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clin Med Res. 2007 Mar;5(1):19–34

Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013 Aug;9(1):30.

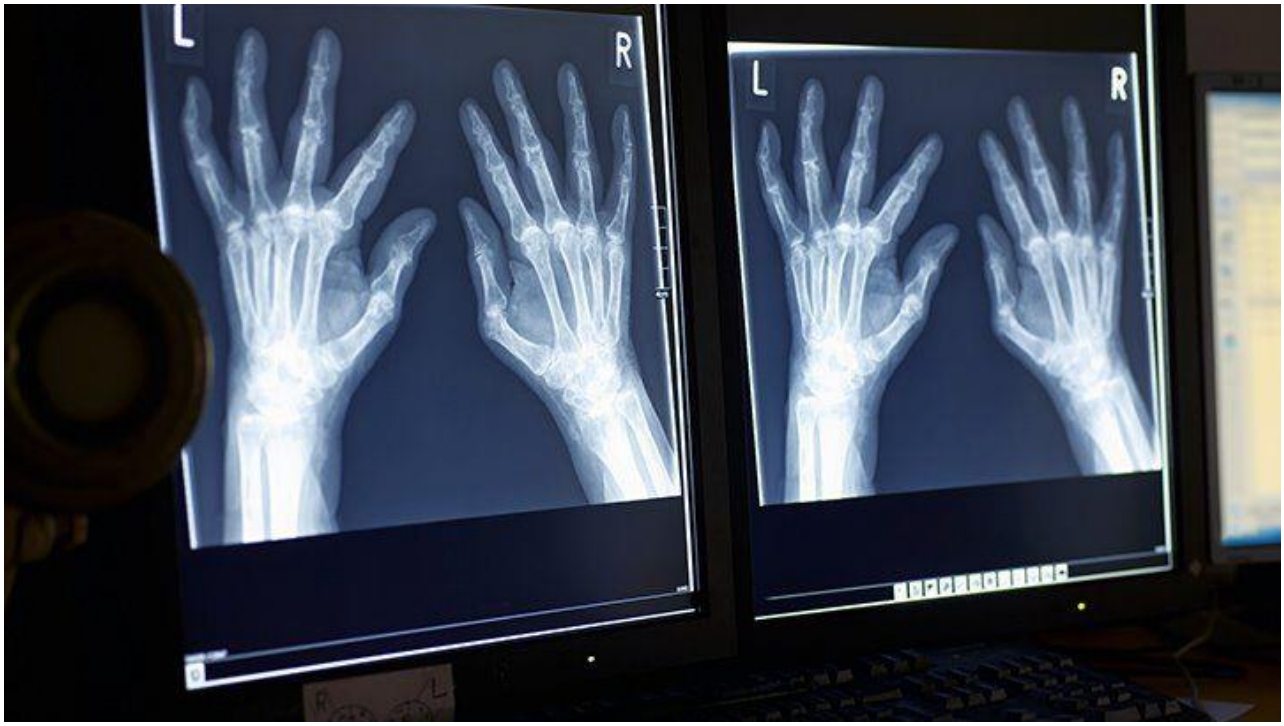
• Blood exams: Erythrocyte sedimentation rate (ESR, also known as sed rate) or C-reactive protein (CRP) levels are frequently elevated in rheumatoid arthritis patients, which may indicate the presence of an inflammatory process in the body. Rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies are two additional common blood tests.[5]



Imaging exams

X-rays may be suggested by your doctor as a way to monitor the development of rheumatoid arthritis in your joints over time. Your doctor can assess the degree of the disease in your body with the aid of MRI and ultrasound.

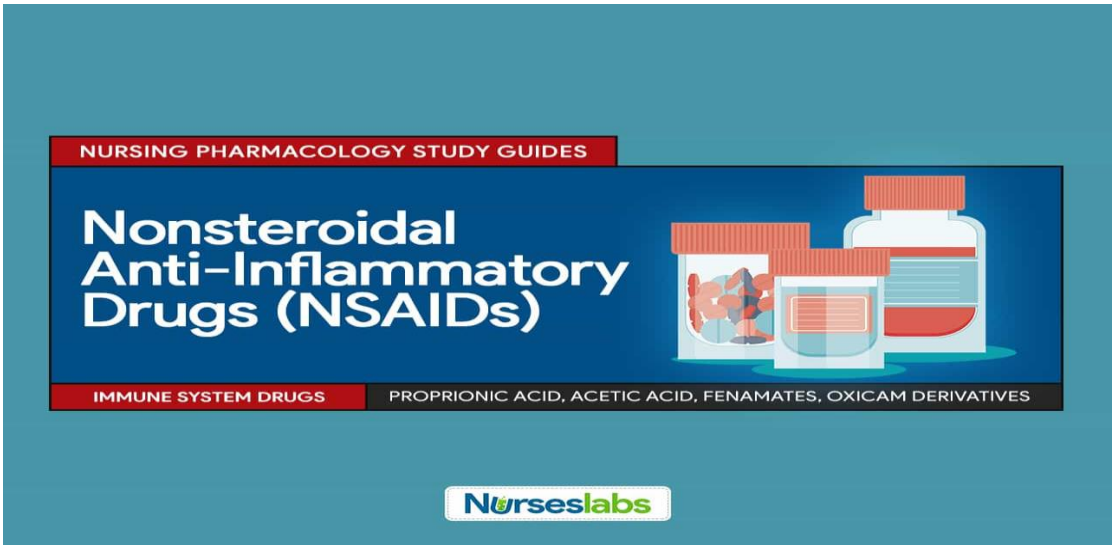
[5]**(Reference):** Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010 Jun;69(6):964–75.



Rheumatoid arthritis has no known treatment. However, clinical studies show that early treatment with drugs known as disease-modifying ant rheumatic drugs (DMARDs) increases the likelihood of symptom remission.[٦]

[6] **(Reference):** Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, Warrington KJ, Davis JM, Hunder GG, Therneau TM, Gabriel SE. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. Arthritis Rheum. 2011 Mar;63(3):633-9. [PMC free article] [PubMed]

7- Treatment



Medication

Steroids. Anti-inflammatory drug and different steroid hormone medicine reduce pain and inflammation whereas additionally retardation joint deterioration. Diabetes, weight gain, and bone weakening square measure potential aspect effects. So as to promptly alleviate symptoms, doctors oftentimes dictate a steroid hormone with the intention of bit by bit truly fizzling out the drug.

Traditional DMARDs

Traditional DMARDs These medications will stop the evolution of rheumatism and forestall irreparable injury to the joints and different tissues. Methotrexate sodium (Trexall, Otrexup, among others), Arava (Arava), anti-inflammatory drug (Plaquenil), and sulfasalazine square measure samples of common DMARDs (Azulfidine). Among the numerous potential aspect effects embrace serious respiratory organ infections and liver injury.

Conventional synthetic DMARD	ATC code
Methotrexate	L04AX03/L01BA01
Sulfasalazine	A07EC01
Hydroxychloroquine	P01BA02
Leflunomide	L04AA13
Azathioprine	L04AX01

Biologic agents. This more recent class of DMARDs, also referred to as biologic response modifiers, consists of the drugs abatacept (Orencia), adalimumab (Humira), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), rituximab (Rit)

Biologic DMARDs In most cases, biologic DMARDs work best when combined with a traditional DMARD, like methotrexate.

The danger of infections is also increased by this class of medication.

Targeted synthetic DMARDs. DMARDs with a specific target.

If conventional DMARDs and biologics have failed, you may turn to baricitinib (Olumiant), tofacitinib (Xeljanz), and upadacitinib (Rinvoq).

Increased tofacitinib dosages can raise the risk of lung blood clots, life-threatening cardiac problems, and cancer.

Surgery If medicine square measure unable to prevent or slow joint injury, you and your doctor could think about surgery to revive broken joints. Your doctor could refer you to a physical or activity healer United Nations agency will train you. Your ability to maneuver your joint is also restored with surgery. It may also enhance performance and reduce pain. One or a lot of the subsequent ways is also used throughout surgery for creaky arthritis:

Synovectomy Pain relief and enhanced joint flexibility could result from surgery to get rid of the inflammatory synovial membrane.

Tendon restoration sinews close your joint could rupture or become loose thanks to joint injury and inflammation. The tendons around your joint can be ready to be repaired by your doctor.

Fused joints. Once a joint replacement isn't A possibility, surgically fusing a joint is also suggested to stabilise or aline a joint similarly on relieve discomfort.

Replacement of each joint. Your doctor can take away the broken joint elements throughout a joint replacement procedure and replace them with a metal and plastic corrective. The risks of hemorrhage, infection, and pain related to surgery. The benefits and hazards together with your doctor.[7]

[7] **(Reference):** Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of rheumatoid arthritis in Sweden: a nationwide population-based assessment of incidence, its determinants, and treatment penetration. Arthritis Care Res (Hoboken). 2013 Jun;65(6):870-8. [PubMed]

Frisell T, Holmqvist M, Källberg H, Klareskog L, Alfredsson L, Askling J. Familial risks and heritability of rheumatoid arthritis: role of rheumatoid factor/anti-citrullinated protein antibody status, number and type of affected relatives, sex, and age. Arthritis Rheum. 2013 Nov; 65(11):2773-82. [PubMed]

8-Treating rheumatism with herbs and natural methods

Exercising

You can notice the most effective rheumatism exercises with the help of a healer. You'll flex the muscles close to the black-and-blue joints. This could facilitate scale back a number of the symptoms of rheumatism. Exercises that strengthen the muscles round the afflicted joints, as well as swimming and athletics, would possibly reduce the whole impact on the joints and slow the course of rheumatism.

Use heat and cold compresses

Medical analysis on the benefits of applying heat or cold to treat rheumatic pain is contradictory. Once these painful locations square measure heated or cooled, some individuals expertise fleeting alleviation. You can apply heat or cold compresses to the affected space reception before resting.

Modification in life-style

Some persons with rheumatism could take pleasure in reducing physical and emotional stress, and there square measure many techniques for doing therefore, like yoga, tai chi, and heedfulness meditation.

Maintain a healthy diet

A plant-based diet will improve general health, and people with rheumatism could particularly take pleasure in it. A diet high in contemporary manufacture, whole grains, legumes, nuts, and seeds dramatically lowers inflammation in people who square measure afflicted with it.

Consume dietary supplements

Omega-3 fatty acids, that square measure easy in animal oil, inhibit inflammatory receptors to cut back inflammation. Supplements containing curcumin or turmeric can also be useful in treating inflammatory disease, though people who square measure taking Coumadin ought to avoid turmeric. Probiotics, a supplement that additionally helps with inflammation reduction, square measure gift in numerous yoghurts and pickles, among different food.

Creating use of treatment

In Chinese medication, meridians, that square measure energy lines in your body, square measure aroused with needles. This medical aid tries to balance out energy imbalances and reduce inflammation-related pain.

Aromatherapy

Although the fragrance of lemon might facilitate, this natural cure does not appear to alter the amount of discomfort or the chemicals that turn out inflammation. Whereas essential oils will create a massage a lot of pleasant, you must exercise caution once exploitation them locally as a result of their far-famed skin irritants.

Adhere to training program

You can learn to manage natural reactions like your pulse and pressure level with the help of this technology. By swing sensors on your body that convey information to a monitor, you'll be able to use this technology that successively teaches you the way to regulate your reaction to worry and so scale back pain.

Treatment of rheumatism with herbs

Potential herbal and natural methods of treating rheumatism include the following:[8]

Scientific classification	
Kingdom:	Plantae
Clade:	Tracheophytes
Clade:	Angiosperms
Clade:	Monocots
Clade:	Commelinids
Order:	Zingiberales
Family:	Zingiberaceae
Genus:	*Zingiber*
Species:	***Z. officinale***
Binomial name	
Zingiber officinale Roscoe[1]	

1. Ginger

It is an herb traditionally used to treat colds, indigestion, migraines, and high blood pressure? It is also known for its anti-inflammatory effects, so it is worth mentioning when talking about herbal treatment for rheumatism. A study published in 2014 reports that ginger has the ability to help symptoms of rheumatoid arthritis. You can drink up to four cups of ginger tea per day, but people who take blood thinners or who have gallstones should not take ginger.[9]

[8] **(Reference):** Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum. 1987 Nov;30(11):1205-13. [PubMed]

Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, Kumagai S. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2010 Jan;69(1):70-81. [PubMed]

[9] **(Reference):** Philippou E, Nikiphorou E. Are we really what we eat? Nutrition and its role in the onset of rheumatoid arthritis. Autoimmun Rev. 2018 Nov;17(11):1074-1077. [PubMed]

2. Green tea

A recent study in mice found that green tea may contain an active compound that reduces inflammation and swelling, as it is considered an herbal treatment for rheumatism. You can drink 4-6 cups of green tea a day, but always check with your doctor before introducing green tea into your diet, as green tea is known to interact negatively with some medications.

3- Rosemary

Kingdom:	Plantae
Clade:	Tracheophytes
Clade:	Angiosperms
Clade:	Eudicots
Clade:	Asterids
Order:	Lamiales
Family:	Lamiaceae
Genus:	Salvia
Species:	S. rosmarinus
Binomial name	

Salvia **genus** **Rosmarinus**

One of the potent plants that can be used to cure rheumatism is rosemary. It is used to lessen joint discomfort and enhance the immune system since it includes a high amount of vitamins and nutrients, including calcium and iron. To feel better, you can boil it in a glass of water and drink it.[10]

4- Aloe vera

It is a plant with a widely known name, however few folks square measure attentive to its varied healthful uses and advantages. Aloe juice is suggested as a result of it helps to spice up the system and soothe pain whereas additionally being a superb medical aid for several ailments, as well as rheumatism. It's utilized during a kind of commodity, like drinks, lotions, ointments, and gels for delicate burns and sunburns. For aloe extract's efficaciousness or safety as a topical medication or cosmetic, there's scant clinical proof.[11]

[1] **(Reference):** Qin B, Yang M, Fu H, Ma N, Wei T, Tang Q, Hu Z, Liang Y, Yang Z, Zhong R. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. Arthritis Res Ther. 2015 Mar 29;17:86. [PMC free article] [PubMed]

1(**Reference):** Li X, Sundquist J, Sundquist K. Socioeconomic and occupational risk factors for rheumatoid arthritis: a nationwide study based on hospitalizations in Sweden. J Rheumatol. 2008 Jun;35(6):986-91. [PubMed]

5- Turmeric

Turmeric

Inflorescence of *Curcuma longa*

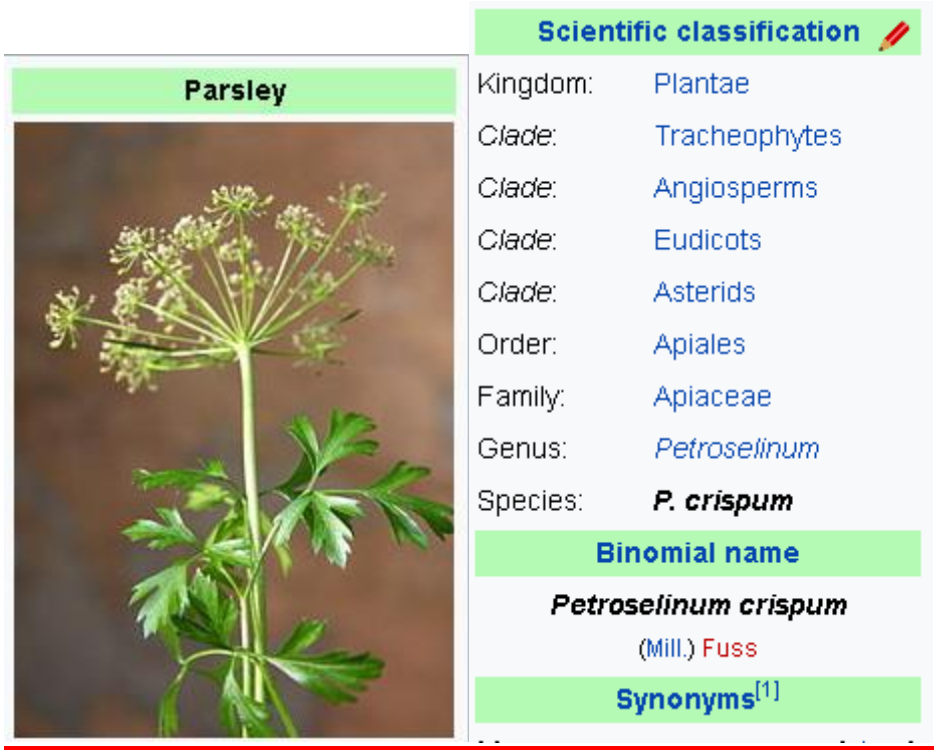
Turmeric rhizome and powder

Scientific classification	
Kingdom:	Plantae
Clade:	Tracheophytes
Clade:	Angiosperms
Clade:	Monocots
Clade:	Commelinids
Order:	Zingiberales
Family:	Zingiberaceae
Genus:	*Curcuma*
Species:	***C. longa***

Binomial name

Many people square measure unaware of the advantages of turmeric for health and healing; they solely knowledge to employ it in food. Take it a day. Turmeric powder has associate degree earthy, mustard-like scent and a heat, bitter, black pepper-like flavour. The Food and Drug Administration and also the World Health Organization have all given their seals of approval to the intense yellow chemical curcumin that is created by the turmeric plant.

6- Parsley



Parsley contains several vitamins like fat-soluble vitamin, C, K, and E. It additionally contains variety of nutrients like phosphoric, zinc, copper, calcium, iron and different parts that job to stop rheumatic pain and inflammatory disease, wherever parsley leaves will be poached In water, then drink this drink to feel higher.[12]

[1] **(Reference):** De Roos AJ, Koehoorn M, Tamburic L, Davies HW, Brauer M. Proximity to traffic, ambient air pollution, and community noise in relation to incident rheumatoid arthritis. Environ Health Perspect. 2014 Oct;122(10):1075-80. [PMC free article] [PubMed]

7- Chamaemelum nobilis

Chamomile is one amongst the natural herbs that plays a charming role in treating joint and bone pain, because it could be a powerful medicine, wherever Chamaemelum nobilis tea will be ready like regular tea, and drink from it endlessly till recovery.[13]

[1] **(Reference):** Wegner N, Lundberg K, Kinloch A, Fisher B, Malmström V, Feldmann M, Venables PJ. Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. Immunol Rev. 2010 Jan;233(1):34-54. [PubMed]

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Skin cancer

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1 Contents

2 Introduction

Skin organ is the largest organ in the human body. It is considered It is the body's first line of defense. It always exposed to different types of agents such as sun damage and micro-organisms[1]. So, these agents act as carcinogenic substances which stimulate skin cancer. The most common skin cancer presents at the United States of America[2]. In USA, there are 9500 new cases of skin cancer every day, and there are two cases of death due to skin cancer every hour[3, 4]. At least, one over 5 people at USA will develop skin cancer by age of 70[2]. The rate of non-melanoma increased due to ultraviolet rays of sun [5]. In addition, there are more than 5.4 million treated cases of nonmelanoma skin cancer[3]. Skin cancer costs 8.1 billion dollar each year at united states of America [6]. The rate of diagnosis and treatment of skin cancer has been increased by 77% between 1994 and 2014 [7].

3 Definition

Skin cancer is multiple stages consists of cancer initiation, promotion and progression[8]. Initiation stage starts after exposure to ultraviolet rays which cause the damage of skin DNA. These ultraviolet rays cause the damage of DNA by both ways, directly by DNA damage by photons and indirectly by its reactive oxidative stress on DNA, membrane, and protein[9]. If DNA remains unrepaired, it will lead to the next stage through which cell undergoes irreversible permanent genetic mutations, enabling the cell with the ability for autonomous growth[10]. Finally, the progression stage the benign tumor will undergo further genetic mutations and

becomes progressively invasive, transforming into a malignant neoplasm with the ability to metastasize[8].

4 Risk factors [11]

Risk factors for skin cancer are identical to those of other skin cancers (sun exposure, fair complexion, light eyes) but also include:

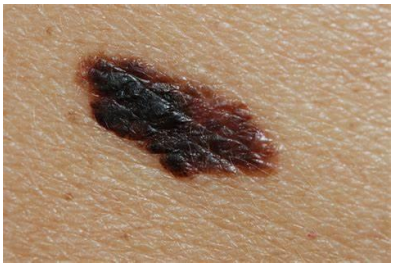
- Family history in first-degree relatives
- Ionizing radiation
- Chronic arsenic exposure
- Excessive sun exposure
- One or more atypical nevi
- Light skin
- History of sunburns
- Tanning bed exposure
- Older age

Risk Factors for the recurrence of Cutaneous Squamous Cell Carcinoma depend on Location, Size, poorly defined borders, recurrent tumors, moderately or poorly differentiated tumors, rapidly growing tumors, immunosuppressed patient, depth greater than or equal to 2 mm or Clark level IV–V9, site of previous radiation therapy or chronic inflammation, neurologic symptoms, adenoid, adenosquamous, or desmoplastic subtypes, and perineural or vascular involvement

5 TYPES OF SKIN CANCER

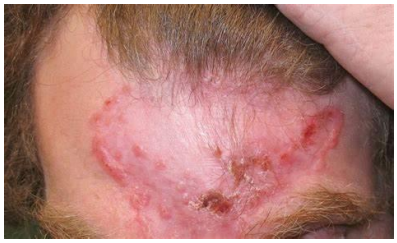
Skin cancer is commonly categorized as malignant melanoma, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) as the major subtypes.

1. **Malignant melanoma:** Malignant melanoma occurs at epidermal melanocytes and occurs at any tissue which contains melanocytes, it occurs at the skin surface, so it is easily detected by necked eyes.



Malignant melanoma

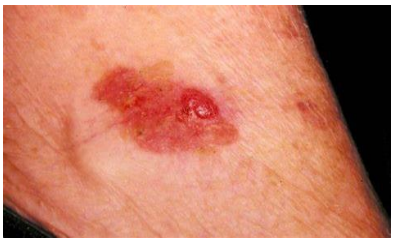
2. **Basal cell carcinoma (BCC):** BCC produced at basal cells [12] . approximately 80% of basal cell carcinoma occurs at head and neck [13]. BCC lesions start as small papules that may enlarge slowly over months to years which are shiny papules with pearly borders and central ulcers. BCC is associated with ambiguous symptoms such as itching and tenderness so it may be mistaken by patients as pimples [14].



Basal Cell Carcinoma (BCC)

3. **Squamous cell carcinoma (SCC):** SCC occurs at epidermal keratinocytes that invades the dermis. SCC may cause massive tissue destruction and metastasis through hematogenous and lymphatic spread [15].

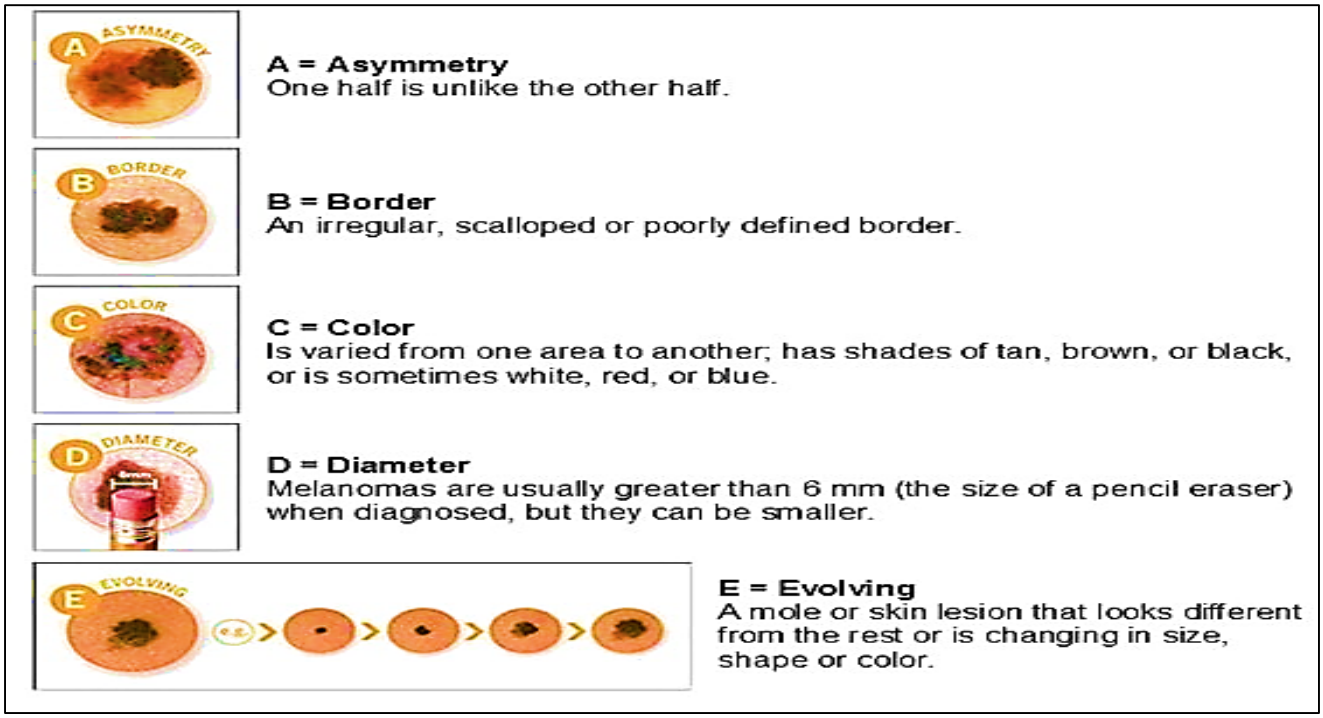
Clinical picture of the disease is highly variable including papules, plaques, or nodules, and smooth, hyperkeratotic (crusty), or erosive lesions [16].



Squamous Cell Carcinoma (SCC)

6 Diagnosis

There are different methods for the diagnosis of skin cancer, which differ according to type of skin cancer. The most important method for each doctor which is important to know is ABCDE tools for detection of early melanoma [17].



ABCDE tools for detection of early melanoma[17].

7 Treatment

1. **<u>Surgical and radiological management of skin cancer</u>**

- **Management of nonmelanoma skin cancer**

Table 2. Treatments for Nonmelanoma Skin Cancer

Treatment	*Advantages*	*Disadvantages*	*Most appropriate use*
Superficial ablative techniques			
Electrodesiccation and curettage, cryotherapy	Minimal equipment needed Normal tissue spared	No histologic margin control Slow healing by secondary intention Potential suboptimal scarring	Tumors at low risk of recurrence
Full thickness			
Excision	Histologic margin control Rapid healing with primary repair	Lack of normal tissue conservation	Tumors at low or moderate risk of recurrence
Mohs micrographic surgery	Microscopic margin control Highest cure rates Conservation of normal tissue	Expensive Limited availability	Tumors at moderate or high risk of recurrence Larger tumors Tumors with more invasive histologic subtype Tumors in locations where conservation of normal tissue is important
Radiotherapy	Favorable cosmetic results	No histologic margin control Expensive Not appropriate for younger patients because of poor long-term cosmesis	Tumors at high risk of recurrence but not amenable to surgery Recurrent tumors Older patients

Adapted with permission from Martinez JC, Otley CC. The management of melanoma and nonmelanoma skin cancer: a review for the primary care physician. Mayo Clin Proc. *2001;76(12):1258.*

This diagram shows the stages of management of nonmelanoma skin cancer and the advantages and disadvantages of each type [16]

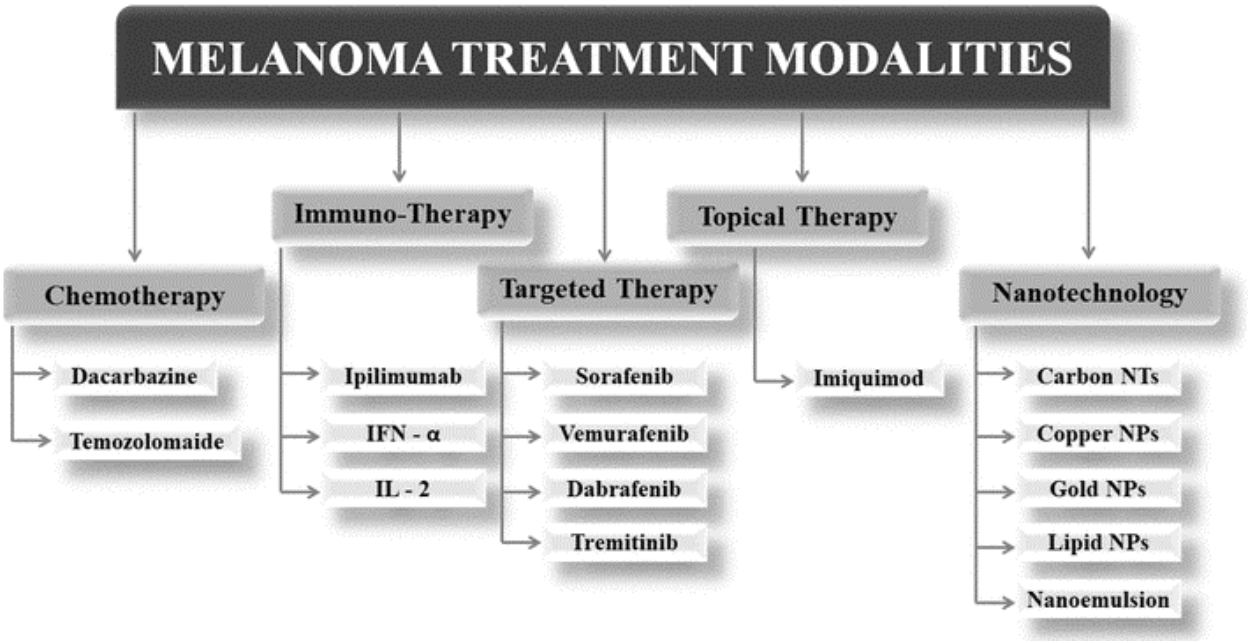
- **Management of melanoma skin cancer**

Stage	Definition	Treatment options
1	Tumour less than 2cm diameter, no metastasis	Wide local excision Radiotherapy
2	Tumour 2-4cm diameter, no metastasis	Wide local excision (LN removal advised) Radiotherapy Adjuvant immunotherapy
3	Tumour more than 4cm diameter and/or metastatic to regional lymph node but not metastatic to distant sites	Wide local excision and LN removal Radiotherapy Adjuvant immunotherapy
4	Distant metastasis present	Immunotherapy Chemotherapy Tyrosine kinase inhibitor therapy Palliative care

This table show different options in the management of melanoma skin cancer according to stages of melanoma [18]

2. Medical management

- **Non phytotherapy**

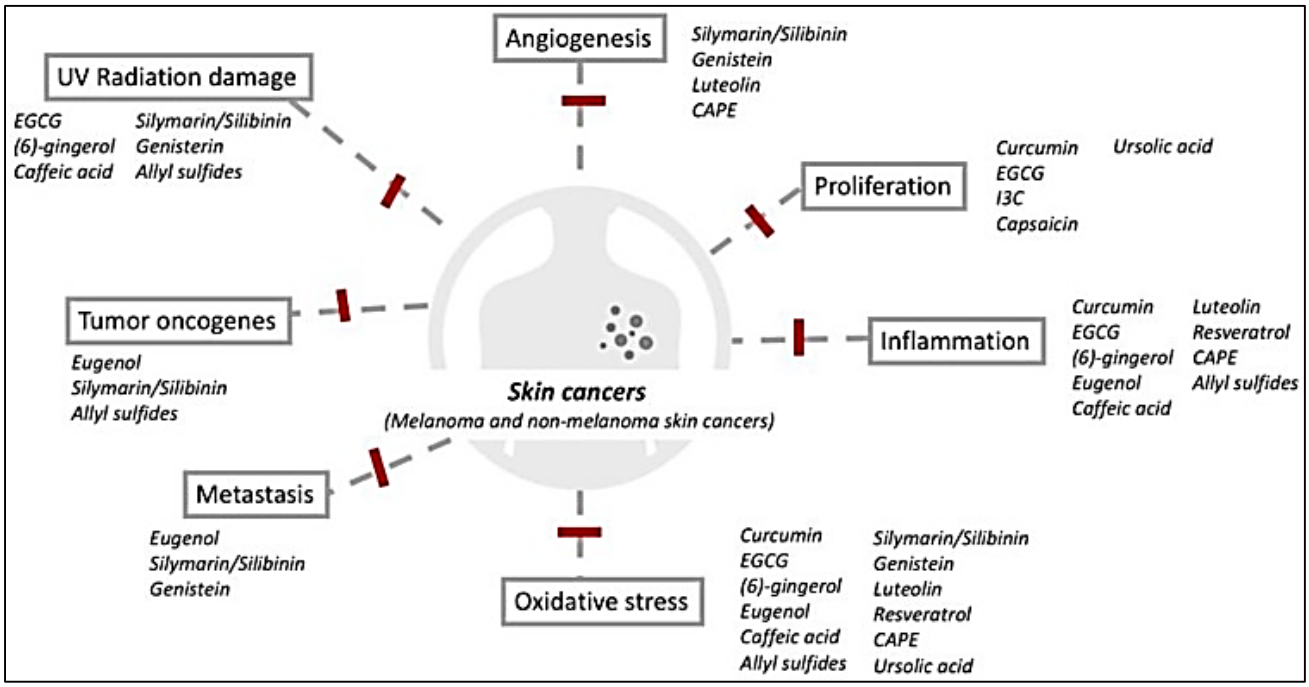


Classification of melanoma treatment modalities [19].

- **Phytotherapy:**

Herbal medicine plays an important and unique role in the management of skin cancer, especially that the cancerous and precancerous lesions are easy to reach for the patient and the doctor. Therefore, it is easy to apply topical drugs unlike the treatment of other types of cancers that require oral treatment, which results in systemic side effects. Secondly, skin injuries and their treatment are easy to assess by the doctor and the patient. Third, the side effects of topical medications are obvious to the patient, so they can be treated as soon as they appear, and thus the incidence of serious side effects is reduced. Therefore, clinical trials seek to develop the efficacy of topical medicine due to their advantages over other

medicines. So, several promising phototherapeutics will be present as a resolution of skin cancer problem in a variety of fresh fruits, vegetables, roots, and herbs, such as epigallocatechin-3-gallate, resveratrol, curcumin, proanthocyanidins, silymarin, apigenin, capsaicin, genistein, indole-3-carbinol, and luteolin. They used for the improvement of skin cancer by several mechanisms as shown in the following figure.



Phototherapeutics in the chemoprevention of melanoma and non-melanoma skin cancers[20]

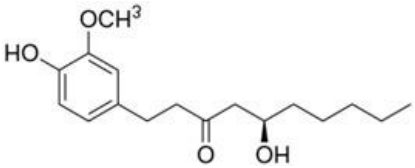
1. **<u>Zingiber officinale ginger</u>**

   Category: Phenolic compounds

   Phytochemical: (6)-gingerol

   Source: Ginger

Structure: (1-[4′-hydroxy-3′-methoxyphenyl]-5-hydroxy-3-decanone)



root of the Zingiber officinale ginger

Usable part of plant: root of the Zingiber officinale ginger plant

Scientific effect: according to park et al, topical application of (6)-gingerol significantly inhibited skin melanoma formation[21], it also has an anti-inflammatory effect[21, 22], and anti-oxidant effect[23]

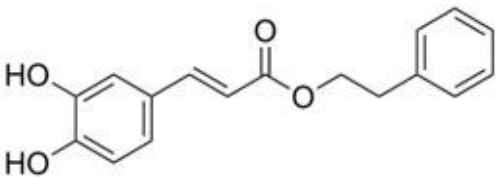
2. Honeybee propolis

Category: Phenolic compounds

Source: Honeybee propolis

Phytochemical: Caffeic acid phenethyl ester (CAPE)

Structure:



Scientific effect: CPAE is a major component of propolis which is derived from honeybee products. This product has an inhibitory effect of many types of cancer

such as colon cancer, lung cancer, pancreatic cancer, melanoma, and glioma[24-28]. In addition, it significantly inhibited the skin papilloma on mice. It also downregulated the vascular endothelial growth factor and multidrug resistance 1, is a protein associated with anti-cancer drug resistance[29]. Other effects of CPAE are anti-mitogenic, anti-inflammatory, anti-carcinogenic, and immunomodulatory properties in vitro[30].

Honeybee propolis

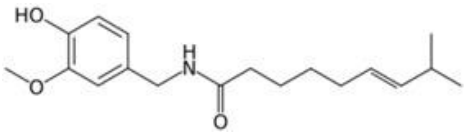
3. Capsicums

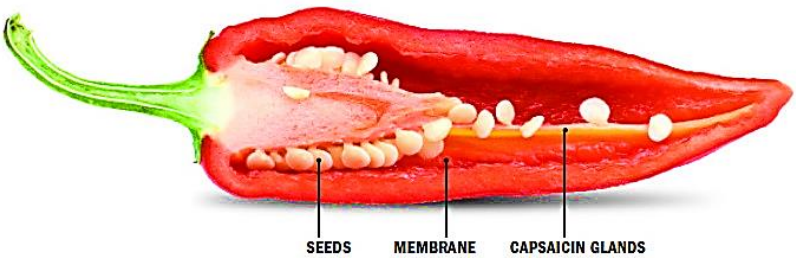
Category: Phenolic compounds

Phytochemical: Capsaicin

Source: Red chili, peppers, and jalapenos

Structure: trans-8-methyl-N-vanillyl-6-nonenamide





Capsaicin

Usable part of plant: capsaicin glands

Scientific effect: capsaicin is one of the most used species worldwide. There is a conflict about the role of capsaicin as anti-cancer or as a chemotherapy[31].

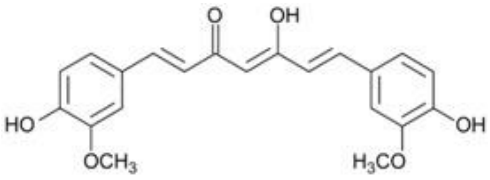
Hwang et al. found that capsaicin has a pro-carcinogenic effect in mice by activation of the tyrosine kinase epidermal growth factor receptor and COX-2[32], but park et al. reported the opposite finding. They reported that the capsaicin has no significant increase in the growth of mouse skin tumors but also it inhibited papilloma formation in mice[33]. In addition, it is found that the capsaicin promote the apoptosis in human cutaneous squamous cell carcinoma cell[34].

4. Golden spice turmeric (Curcuma longa)

Category: Phenolic compounds

Phytochemical: Curcumin (diferuloylmethane)

Source: Turmeric

Structure: 

Golden spice turmeric (Curcuma longa)

Usable part: rhizome of the golden spice turmeric

Scientific effect: curcumin has anti-inflammatory and antioxidant effect at different types of inflammatory diseases such as Crohn's disease, ulcerative colitis, psoriasis, and atherosclerosis[35]. It also has a protective mechanism against various types of cancer such as head and neck squamous cell carcinoma, lung cancer, pancreatic cancer, colorectal cancer, prostate cancer, and multiple myeloma [35].

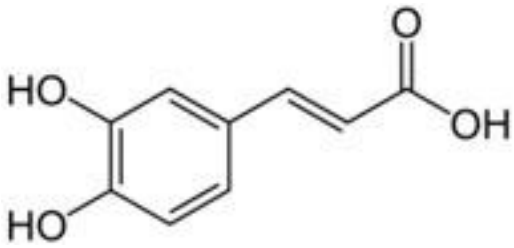
5. **Coffee**

Category: Polyphenol: phenolic acid

Phytochemical: Caffeic acid

Source: Coffee

Structure: (3,4-dihydroxycinnamic acid, CA)



Scientific effect: bioactive caffeic acid has anti-inflammatory, antioxidant, and anti-cancer properties[36-38]. According to Kang et al, caffeic acid also has an inhibitory effect which prevent the metastasis in the colon cancer [39]. It also inhibited the epithelial–mesenchymal transition in human malignant keratinocytes[40].

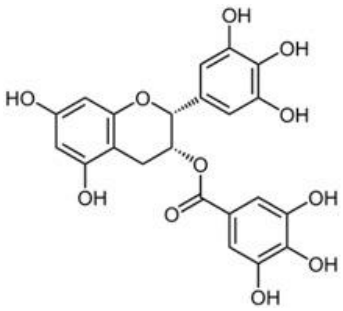
Coffee beans

6. Green tea

Category: Polyphenol: flavonoid

phytochemical: Epigallocatechin-3-gallate

Source: Green tea



Structure:

Scientific effect: Epigallocatechin-3-gallate (EGCG) is the most studied as a chemo-preventive component of green tea phenol due to its antioxidant, anti-inflammatory, and anti-proliferative properties [41]. Katiyar et al. found that Epigallocatechin-3-gallate decreased the skin tumor burden with decreased epidermal edema and hyperplasia[42]. They found also; it has antioxidant effect on human skin by topical application[43].

7. Soybean

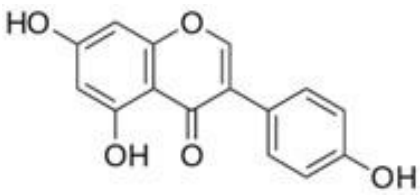
Category: Polyphenol: flavonoid

Phytotherapy: Genistein

Soybean

Source: Soybean

Structure: 4′,5,7-trihydroxyisoflavone



Scientific effects: soybean used for longtime as dietary supplements for osteoporosis, cardiovascular disease, and cancers [44]. Genistein is the most prominent phytoestrogen compound in soybeans and has anti-inflammatory, antioxidant, and anti-proliferative effects[45-47]. It also has a protective properties against various types of cancer such as breast cancer and neuroblastoma, as well as both melanoma and non-melanoma skin [48, 49].

8 Prevention [50]

According to centers of disease control and prevention (CDC), measures of skin cancer prevention including two ways such as following sun safety practices and avoiding indoor tunning.

For practice sun safety, we should stay in the shade, wear clothing that covers your arms and legs, wear a hat with a wide brim to shade your face, head, ears, and neck, wear sunglasses that wrap around and block both UVA and UVB rays, and use a broad-spectrum sunscreen with a sun protection factor (SPF) of 15 or higher.

Indoor tanning means using a tanning bed, sunbed, booth, or sunlamp to darken the skin, these tools make the skin exposed to high levels of ultraviolet rays. Exposure to UV rays for long time make people highly suitable for cataract, skin and eye cancer.

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