Synthesis Review on Filariasis and its prevention by phytochemicals


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Abstract

Filariasis is commonly known as elephantiasis. Elephantiasis is a disease that is characterized by the thickening of the skin and underlying tissues, especially in the legs, male genitals and female breasts [1]. The other terms used for elephantiasis are Elephantiasis Arabum, Bunceemia, Barbadoes leg, Cochin leg and Egyptian saccocèle [2]. Indians were of the first to have known the disease Slipada (sli = elephant, pada = leg), as presented in the Sushruta Samhita. The term was later used by the Roman medical encyclopedist Celsus (ca 30 BC–38 AD), To the Greeks including Hippocrates (ca 460–370 BC), Galen (129–200 AD), and Paulus Aegineta (625–690 AD) the term elephantiasis was associated with ambiguity, implying both filariasis and leprosy [3]. It was not until 807–870 AD that Ali ibn Sahl Rabban al-Tabbari first described elephantiasis as Daa al-Fil (daa = disease, fil = elephant) and denoted treatments in Firdows al-Hikmat (Paradise of Wisdom), the first existent medical book in medieval Persia [4]. Other medieval Persian physicians such as Rhazes (ca 865–925), Akhawayni (9–983), Haly Abbas (930–994), Avicenna (981–1037), and Jorjani (1042–1137) followed al-Tabbari’s concept of elephantiasis in their medical books [5][6][7]. Altogether, the first authentic records of elephantiasis and its related signs, symptoms, and treatment can be attributed to ancient India, Greece, and particularly medieval Persia much earlier to the 16th century. This paper represents the review on Filariasis and its prevention by phytochemicals.

Introduction

Lymphatic Filariasis causes alterations in the lymphatic system and the abnormal enlargement of body parts, causing pain and severe disability [8]. Lymphatic filariasis is a mosquito-borne parasitic disease caused by three species of tissue dwelling filarial nematodes. Wuchereria bancrofti is responsible for 90% of cases and is found throughout the tropics and in some sub-tropical areas world-wide. Brugia malayi is confined to Southeast and Eastern Asia, Brugia timori is found only in Timor and its adjacent islands [5]. Lymphatic filariasis has been identified by the World Health Organisation (WHO) as the second leading cause of permanent and long-term disability world-wide [149]. In addition to the medical problems, there are severe social and psychological consequences, especially in those who suffer from elephantiasis or hydrocele [9][10][148]. Lymphatic filariasis also has a huge economic impact upon endemic communities. In addition to the direct costs incurred in medical or surgical treatment, there are the enormous indirect costs resulting from reduced work capacity and labour loss [148]. The causative organisms: Wuchereria bancrofti

Of the three lymphatic filarial species known to infect humans, W. bancrofti has the widest distribution. It is prevalent in Sub-Saharan Africa, South and Southeast Asia, and introduced to countries in the Caribbean and Latin America with the slave trade [11]. As dioecious worm, W. bancrofti exhibits sexual dimorphism. The adult worm is long, cylindrical, slender, and smooth with rounded ends. It is white in colour and almost transparent. The body is quite delicate making it difficult to remove from tissues. It has a short cephalic or head region connected to the main body by a short neck which appears as a constriction. There are dark spots which are dispersed nuclei throughout the body cavity, with no nuclei at

2. *Brugia malayi*

*Brugia malayi* is found in tropical regions of South and Southeast Asia, overlapping with the range of *W. bancrofti* [11]. In areas where both species are present, they may co-infect the same host, but they do not utilize the same vector species.

Adult worms resemble the classic nematode roundworm. Long and threadlike, *B. malayi* and other nematodes possess only longitudinal muscles and move in an S-shaped motion [21]. Adults are typically smaller than adult *W. bancrofti*. Female adult worms (50 mm) are larger than male worms (25 mm) [Web Atlas of Medical Parasitology].

*B. malayi* microfilariae are 200-275 μm in length and have a round anterior end and a pointed posterior end. The microfilariae are sheathed, which stains heavily with Giemsa. The sheath is actually the egg shell, a thin layer that surrounds the egg shell as the microfilariae circulate in the bloodstream. The microfilariae retain the sheath until it is digested in the mosquito midgut [22]. *B. malayi* microfilariae resemble *W. bancrofti* microfilariae with minor differences that can aid in laboratory diagnosis. *B. malayi* microfilariae can be distinguished by the noncontiguous row of nuclei found in the tip of the tail. There are two terminal nuclei that are distinctly separated from the other nuclei in the tail, whereas the tail of *W. bancrofti* contains no nuclei. *B. malayi* microfilariae also have a characteristic cephalic space ratio of 2:1 [WHO, 1997].

Two major forms of *B. malayi* have been recognized: anthropophilic and zoophilic [23]. Anthropophilic *B. malayi* are transmitted by *Anopheles* mosquitoes that breed in open swamps or left over rice wastes, restricting this form of the parasite to rural areas [24][25][23] [41]. In accordance with the biting habits of the principal vector, anthropophilic strains exhibit nocturnal periodicity and exclusively infect humans. [26]. Zoophilic *B. malayi* are transmitted by *Mansonella* mosquitoes. These strains show varying patterns of periodicity, but are mainly nocturnally sub periodic. In Southeast Asia, they are readily passed between humans and wild and domestic animal hosts by their zoophilic vectors [27].

3. *Brugia timori*

*B. timori* has the most restricted geographic range of the lymphatic dwelling filarial species. It is only found in Indonesia and Timor-Leste, where it replaces *B. malayi* in areas east of the Wallace line. *B. timori* is biologically similar to nocturnally periodic *B. malayi* in its Microfilaria periodicity, use of an Anopheline vector, and in its restriction to human definitive hosts. Like *B. malayi*, this species may be co-endemic with *W. bancrofti* and may co-infect the same human host, but the two parasites are transmitted by different vector species. For example, on Alor Island *W. bancrofti* is transmitted by *A. subpictus* in coastal areas while *B. timori* is transmitted by *A. barbirostris* near rice patties [26].

Life cycle of the filarial parasite.

Filarial parasites carry out their life cycle in two hosts. Human beings serve as the definitive host and mosquitoes as their intermediate hosts. The adult parasites reside in the lymphatic system of the human host. They are found mostly in the afferent lymphatic channels of the lymph glands in the lower part of the body. The first-stage larvae, known as microfilariae, are present in circulation. The microfilariae have a membrane sheath, are found mainly in the peripheral blood at peak amounts from 10 p.m. to 4 a.m. They migrate between the deep and the peripheral circulation exhibiting unique diurnal periodicity. During the day, they are present in the deep veins,
and during the night, they migrate to the peripheral circulation. The cause of this periodicity remains unknown, but the advantages of the microfilariae being in the peripheral blood during these hours may ensure the vector, the nocturnal mosquito, having a higher chance of transmitting them elsewhere. Physiological changes also are associated with sleeping, such as lowered body temperature, oxygen tension and adrenal activity, and an increased carbon dioxide tension, among other physical alterations, any of which could be the signals for the rhythmic behavior of microfilarial parasites. If the hosts sleep by day and are awake at night, their periodicity is reversed. In the South Pacific, where parasite shows diurnal periodicity, it is known as periodic.

The microfilariae are transferred into a vector, which are most commonly mosquito species of the genera Culex, Anopheles, Mansonia, and Aedes. Inside the mosquito, the microfilariae mature into motile larvae called juveniles. When the infected mosquito has its next blood meal, parasite is egested via the mosquito’s proboscis into the blood stream of the new human host. The larvaemove through the lymphatic system to regional lymph nodes, predominantly in the legs and genital area. The larvae develop into adult worms over the course of a year, and reach sexual maturity in the adherent lymphatic vessels. After mating, the adult female worm can produce thousands of microfilariae that migrate into the blood-stream. When a mosquito vector bites the infected human host, it ingests the microfilariae, and thus repeat the lifecycle [13] [29] [30]. Development and replication of filarial parasite occurs in two discrete phases: in the mosquito vector and in the human. Both stages are essential to the life cycle of the parasite.

Wolbachia in filarial nematodes

Starting from the mid-1970s, electron microscopy studies showed the presence of intracellular bacteria in the body of various species of filarial nematodes, including Onchocerca volvulus, Dirofilaria immitis, Litomosoides sigmodontis and Brugia malayi [34] [35] [36]. The bacteria were observed in the lateral chords of both males and females, in the reproductive apparatus of females (i.e. in the oogonia, oocytes, embryos and microfilariae) and also in the larvae present in the mosquito vector. These observations were strongly suggestive of transovarial transmission of the bacteria. Two decades after these observations, based on DNA sequence data, the bacteria of filarial nematodes have been identified as belonging to Wolbachia [37] [38] [39]. Wolbachia bacteria are widespread in filarial nematodes: almost all the filariasis agents of humans and animals have been shown to harbour these bacteria. Infected species include O. volvulus, O. ochengi (and other species of the genus Onchocerca), D. immittis, D. repens, B. malayi, B. pahangi, Wuchereria bancrofti, Mansonella ozzardi and L. sigmodontis [40] [39] [42] [40]. Wolbachia in filarial nematodes is maternally transmitted. In addition, in filarial species positive for Wolbachia, the prevalence of the infection appears 100% [43].

Clinical Manifestation of Lymphatic Filariasis

Clinical Manifestations of Lymphatic filariasis (LF) are influenced by number of cofactors, including patient’s age and gender, the species and strain of parasite, anatomical location of the adult worms, immune response to the parasite, and secondary bacterial infections (Friedman and Kalisher 2002). The clinical manifestations of the disease are due to the inflammation and damage of lymphatic vessels. Most infections do not produce symptoms, but in people where the lymphatic drainage is badly impaired, the common symptoms include hydrocele (swelling of the scrotum), swelling of the
legs and feet, and thickening of the skin into folds. Lymphedema is a common clinical manifestation of LF. Filariasis due to W. bancrofti involves the entire limb, the genitals, or breasts, whereas B. malayi infection differs in that the lymphedema involves only the legs below the knee and upper limbs below the elbow, without any genital or breast involvement [44].

Acute Clinical Manifestation

The most common acute clinical manifestations in LF are adenitis (inflammation of a gland) and lymphangitis (inflammation of the lymphatic vessels and channels), that are usually associated with chills, fever, and pain in the involved region. Though occasionally seen during the early stages of the disease, these events are more frequent in higher grades of lymphedema. Several factors have been associated with these acute events such as secondary bacterial infection, immunological responses to a variety of filarial antigens, excreted or secreted products by the parasite or exposure to fresh infection with L3, release of substances from death of the adult worm [45]. Acute filarial adenolymphangitis (AFL) is supposed to be caused by death of adult worm either spontaneously or as a result of treatment with a macrofilaricidal drug. Dilatation of the lymphatic vessels induced by the presence of the adult worm eventually leads to lymphatic dysfunction and accumulation of protein-rich fluid in the tissues. Latter may result into recurrent bacterial infections which further leads to the disease. Trauma, interdigital fungal infections, and onchocerciasis provide entry sites for these bacteria, which multiply rapidly and cause a reticular lymphangitis of the small collecting vessels; the condition is known as acute dermatolymphangioadenitis (ADLA) [46]. Which is a major risk factor for the development of elephantiasis [47]. The lymphatics of the male genitalia are frequently affected, leading to funiculitis, epididymitis, and orchitis. Repeated episodes of acute attacks lead to the formation of fibrous and calcified tissues in and around the lymphatic vessels [48].

Chronic Manifestation of Lymphatic Filariasis

Common chronic manifestation of LF is lymphedema of extremities which on progression result into elephantiasis. The upper limbs, male genitalia, and rarely breasts in the females may also be affected. The lymphedema of the limbs is commonly graded as grade I, grade II, and grade III [49]. Grade I is mostly pitting edema; reversible on elevation, grade II lymphedema is mostly nonpitting edema, not spontaneously reversible on elevation while grade III is called elephantiasis which is a gross increase in volume in grade II lymphedema accompanied with dermatosclerosis and papillomatous lesions. The most noticeable symptoms occur due to blockage of lymphatics in the chronic stage leading to the irregular discharge of intestinal lymph (chyle) into the renal pelvis and subsequently into the urine resulting into an incurable stage termed as chyluria [50]. The urine may be milky white in color, particularly after a fatty meal. Chyluria is associated with increased high endothelin-1 (ET-1) level and vascular endothelial growth factor (VEGF) [51] [52]. Hydrocoele is the most frequent chronic manifestation of bancroftian filariasis. Chronic epididymitis, funiculitis (inflammatory swelling of the spermatic cord), and lymphedematous thickening of the scrotal skin are also genital manifestations of chronic bancroftian filariasis [53].

Lymphatic system and lymph pump

The lymphatic system consists of a network of lymphatic vessels and interconnected lymph nodes distributed throughout most of the body, which plays a vital role in the controlled transport of immune cells, antigens, lipids, macromolecules, fluid, and particulate matter in the form of lymph. The transportation of lymph along the lymphatic network is directed from the parenchymal interstitial spaces into the nodes via the afferent lymphatic trunks. It exits the nodes through the efferent lymphatics and travels between the nodes, and eventually the lymph exits the lymphatic system, emptying into the blood in the subclavian vein of the neck. Anatomically, the initial lymphatics are composed of a layer of endothelial cells that are loosely placed but with overlapping edges. These resultant gaps are thought to function as “primary valves” that provide unidirectional fluid flux into lymphatics [54] [55] [56] [57]. The predominant mechanism driving lymph formation and flow appears to be the development of transient fluid pressure gradients between the interstitium, the initial lymphatic, and downstream collecting lymphatics. These gradients occur during variations in the local interstitial fluid pressures due to tissue movement and/or compression [56]. The lymphatic system uses lymph pumps (extrinsic and intrinsic) to provide the energy necessary to overcome the steady state opposing pressure gradients and propels lymph along the lymphatic network [58] [59]. Despite the myogenic origin of these rhythmic lymphatic contractions, many factors have been found to modulate the rate of spontaneous intrinsic pumping. The major lymphatic contraction modulators are physical (e.g. temperature, lymph flow, vessel distension) and chemical stimuli (e.g. endothelium-derived factors, circulating hormones and neurotransmitters) [60] [56] [61] [57]. However, spontaneous contractions can still occur in the absence of these factors. The local physical factors such as stretch/pressure and shear/flow also modulate lymphatic tone and function [62].

Lymphatic remodeling during filariasis

Filarial lymphedema is associated with characteristic alterations of the lymphatic system, including the dilatation of lymphatics with extensive collateral formation, loss of functional valves and retrograde lymph flow [63]. In animals models it has been shown that host immune response is believed to play an important role in establishment of chronic filariasis and secondary bacterial infections are shown to aggravate preexisting filariasis [64] [65]. No direct evidence exists that the immune system kills adult W. bancrofti in vivo in long-term residents of endemic areas. However, the inflammatory host response that either causes the death of worms or is induced by the worms has emerged as a major risk factor for the development of some types of chronic filariasis syndromes, such as hydrocoele, chylocele and chyluria [65]. Lymphatic vessel dilatation is believed to be an early event following antigenic stimulation that occurs when the adult worms are still alive and the offspring larvae are released. Moreover, lymphoscintigraphy studies demonstrate that even patients with subclinical manifestations of the disease exhibit considerable structural abnormal and aberrant patterns of lymph flow [66]. To determine the extent to which lymphatic dilatation occurs in the presence of living adult W. bancrofti, performed longitudinal ultrasonographic measurements in 80 men (mean age 24 years) in Brazil who had a total of 107 W. bancrofti nests detectable by ultrasound. Initial mean lymphatic vessel diameter at the site of the worms was 3.4 mm. During the study period (2–35 months), lymphatic vessel diameter increased at the site of 92 (86.0%) adult worm nests. Mean rate of increase of lymphatic vessel diameter was 1.2 mm per person-year (range, 0.0–9.3 mm per month) [67].

A characteristic feature of long-term filarial infection in humans and animals is the fibrosis and cellular hyperplasia in and around the lymphatic walls. Infection with the parasites for long periods results in the fibrosis of the infected lymph nodes, which eventually become non-functional and are bypassed by new lymphatic vessels [68]. In experimental animal models, irregular large vacuoles, often containing degenerating organelles, have been commonly found in endothelial cells lining Brugia-infected lymphatic vessels. These studies suggest that damage of cells by living or dead worms or worm products may have a direct effect on the endothelial lining of lymphatic vessels and may compromise the efficiency of vessels that collect and transport edematous fluid in affected limbs [69] [70]. The injury possibly makes the lymphatics less effective in transporting edematous fluid and
Molecular mechanisms
Filariasis remains one of the most immunologically complex diseases in humans and the occurrence of filarial parasite associated modulation of the immune response in microfilaric hosts is supported by a large body of clinical evidence as well as animal studies. Filarial patients are known to exhibit strong proinflammatory immune responses and this inflammatory environment is thought to promote the development of physiologic abnormalities of the lymphatic vasculature. Studies in animal models of filarial infection and cellular studies in humans underline the key role played by Wolbachia-derived molecules from filarial parasites in inducing proinflammatory cytokines and thereby initiating an inflammatory response. This inflammatory response to Wolbachia is mediated primarily through Toll like receptors (TLRs). To elucidate the role of TLRs, cytokine responses to different Toll ligands were examined in patients with lymphatic pathology, infected patients with subclinical pathology, and uninfected, normal individuals. Their results suggest an important role for TLR2 and TLR9 mediated pro-inflammatory cytokine induction such as IFN-γ, TNF-α, IL-12 and IL-1β. In addition, activation of both the MAPK and NF-κB pathways are associated in the development of pathology in human lymphatic filariasis. There is also increased expression of the NLR family (Nod like receptor) family of Nod1 and Nod2 in lymphedema patients compared to asymptomatic carriers. These are cytosolic proteins that play a role in NF-κB mediated regulation of proinflammatory pathways are involved in the inflammatory cascade associated with tissue damage in the lymphatics. In addition, individuals with lymphedema also have significantly higher concentrations of interleukin-8, macrophage inflammatory protein -1a, MIP-1β, monocyte chemotactic protein 1, thymus- and activation-regulated chemokine, and interferon-inducible protein 10 in their serum than did uninfected individuals. Innate immune responses that are triggered by the filarial antigen ultimately result in the activation of vascular endothelial growth factors (VEGF), thus promoting lymph vessel hyperplasia as a first step to lymphedema development. The presence of elevated levels of lymphangiogenic factors is associated with the severity of lymphatic pathology. Plasma levels of VEGF-A, VEGF-C and VEGF-R3 are increased with disease progression in filariasis and in clinical cases of lymphedema, hydrocele, and chyluria. VEGF-C induces lymphatic endothelial proliferation and dilation and hyperplasia of the lymphatic vasculature in transgenic mouse models similar to what is observed in the lymphatics of filarial patients. Wolbachia stimulates pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6, and nitric oxide in human patients; these cytokines are known to increase the expression of VEGF-C/VEGFR3, probably by the lymphatic endothelial cells of host lymphatics. In doxycycline-treated patients a significant decrease in serum levels of VEGF-C and VEGFR3 is shown, providing an association between reductions in pro-lymphangiogenic factors and better in LF disease pathology. It has been shown that TLR2-mediated enhancement of angiogenic growth factor production in patients with lymphatic pathology is dependent on mitogen-activated protein kinase (MAPK) and NF-κB signaling. Pharmacological inhibition of either extracellular signal-regulated kinase 1/2 (ERK1/2), p38 MAPK, or NF-κB signaling resulted in significantly diminished production of VEGF-A and Ang-1. Overexpression of lymphangiogenic marker, VEGF-A may cause extravasation and accumulation of fluids, plasma and lymph from blood and lymphatic vessels into the scrotal regions, resulting in the development of hydrocele, chylocele and lymphocele. The presence of circulating immune complexes (ICs), aggregates of antigens, immunoglobulin and complement components is a characteristic feature of human lymphatic filariasis and has been evaluated as a potential non-invasive way of assessing renal damage. The high levels of circulating antigen, in combination with antigen-specific antibodies, activate the complement system in asymptomatic persons, whereas the reduced status of complement activity thereby contributes to the edema and collagen accumulation.
in patients with chronic pathologic changes may increase disease morbidity[89]. Studies in murine models suggest the involvement of both the Th1 and Th2 arms of immunity in resistance to filarial parasites[90][91]. Hence, a compromise in Th1/Th2 effector functions could play a crucial role in establishment and maintenance of chronic, high-density filarial infections without triggering host immune responses as is evident in a majority of asymptomatic cases with circulating microfilariae. Studies in endemic populations suggest that truly endemic normal individuals mount a Th1-like antifilarial immune response, thus remaining infection free. Another hypothesis suggests that the induction and release of Th1 cytokines assist growth and development of filarial larvae and a study shows that live L3 elicit a Th1-like inflammatory response from host cells [92]. Moreover, different life cycle stages of the parasite have been shown to elicit different immune responses. In one such study, the cytokine profile of a group of filaria-infected and uninfected individuals in response to live infective-stage larvae or microfilariae of Brugia malayi, showed significant impairment of both Th1 and Th2 cytokines [75]. Three major networks of immune-regulation and tolerance involving impaired induction of TGF-β and GATA-3 mRNA, were found to be mediating this depressed Th1/Th2 response [91].

Phytochemicals

Phytochemicals are chemical compounds that occur naturally in plants (phyto means “plant” in Greek). Some are responsible for color and other organoleptic properties, such as the deep purple of blueberries and the smell of garlic. There may be as many as 4,000 different phytochemicals. Medicinal plants are the richest bioresource of drugs of traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates and chemical entities for synthetic drugs [93]. The therapeutic use of plants certainly goes back to the Sumerian and the Akkadian civilizations in about the third millennium BC. Hippocrates (ca. 460–377 BC), one of the ancient authors who described medicinal natural products of plant and animal origins, listed approximately 400 different plant species for medicinal purposes. Natural products have been an integral part of the ancient traditional medicine systems, e.g., Chinese, Ayurvedic and Egyptian [94]. According to the World Health Organization, a medicinal plant is any plant which, in one or more of its organs, contains substances that can be used for therapeutic purposes, or which are precursors for chemo-pharmaceutical semi-synthesis. Such a plant will have its parts including leaves, roots, rhizomes, stems, barks, flowers, fruits, grains or seeds, employed in the control or treatment of a disease condition and therefore contains chemical components that are medically active. These non-nutrient plant chemical compounds or bioactive components are often referred to as phytochemicals or phytoconstituents and are responsible for protecting the plant against microbial infections or infestations by pests [95][96][97][99].

Classes of phytochemicals

1. Alkaloids

These are the largest group of secondary chemical constituents made largely of ammonia compounds comprising basically of nitrogen bases synthesized from amino acid building blocks with various radicals replacing one or more of the hydrogen atoms in the peptide ring, most containing oxygen. The compounds have basic properties and are alkaline in reaction, turning red litmus paper blue. In fact, one or more nitrogen atoms that are present in an alkaloid, typically as 1°, 2° or 3° amines, contribute to the basicity of the alkaloid. The degree of basicity varies considerably, depending on the structure of the molecule, and presence and location of the functional groups [94]. They react with acids to form crystalline salts without the production of water [99]. Majority of alkaloids exist as solid such as atropine, some as liquids containing carbon, hydrogen, and nitrogen. Most alkaloids are readily soluble in alcohol and are sparingly soluble in water. The solutions of alkaloids are intensely bitter. These nitrogenous compounds function in the defence of plants against herbivores and pathogens, and are widely exploited as pharmaceuticals, stimulants, narcotics, and poisons due to their potent biological activities. In nature, the alkaloids exist in large proportions in the seeds and roots of plants and often in combination with vegetable acids. Alkaloids have pharmacological applications as anesthetics and CNS stimulants (Madziga et al., 2010).
Glycosides in general, are defined as the condensation products of sugars with a host of different varieties of organic hydroxyl compounds in such a manner that the hemiacetal entity of the carbohydrate must essentially take part in the condensation. Glycosides are colorless, crystalline carbon, hydrogen and oxygen-containing (some contain nitrogen and sulfur) water-soluble phytoconstituents, found in the cell sap. Chemically, glycosides contain a carbohydrate (glucose) and a non-carbohydrate part (aglycone or genin) \[109\] \[99\]. Glycosides are purely bitter principles that are commonly found in plants of the Gentilliaceae family and though they are chemically unrelated but possess the common property of an intensely bitter taste. The bitter act on gustatory nerves, which results in increased flow of saliva and gastric juices. Chemically, the bitter principles contain the lactone group that may be diterpene lactones (e.g., andrographolide) or triterpenoids (e.g., amarogentin). Some of the bitter principles are either used as astringents due to the presence of tannic acid, as antiprotozoan, or to reduce thyroxine and metabolism. Examples include cardiac glycosides (acts on the heart), anthracene glycosides (purgative, and for treatment of skin diseases), chalcone glycoside (anticancer), amarogentin, gentiopicrotin, andrographolide, ailanthone and polygalan. The extracts of plants that contain cyanogenic glycosides are used as flavouring agents in many pharmaceutical preparations. Amygdalin has been used in the treatment of cancer (HCN liberated in stomach kills malignant cells), and also as a cough suppressant in various preparations. Excessive ingestion of cyanogenic glycosides can be fatal. Some foodstuffs containing cyanogenic glycosides can cause poisoning if not properly handled \[94\].

Caffeine has the desired effect of delaying/preventing sleep, but does not affect all people in the same way. It also improves performance during sleep deprivation. In shift workers it leads to fewer mistakes caused by drowsiness. In athletes, moderate doses of caffeine can improve sprint, endurance, and team sports performance, \[107\], but the improvements are usually not substantial. Some evidence suggests that coffee does not produce the performance enhancing effects observed in other caffeine sources \[108\].

Cardiac glycosides are drugs used in the treatment of congestive heart failure and cardiac arrhythmias. Medically important glycosides can be obtained from plants belonging to the Liliaceae (Drimia Ursina), Ranunculaceae (Adonis), Apocynaceae (Strophantus, Thevetia) and Scrophulariaceae (Digitalis) \[110\]. Digitalis purpurea is the most widely studied plant that contains cardiac glycosides. This plant contains digoxin and digitoxin. Digoxin is the most used cardiac glycoside and is now produced by isolation from the related species Digitalis Lanata \[111\].

Cardiac glycosides work by inhibiting the Na+/K+/ATPase leading to an increase in the amount of Ca++ ion intracellular. Elevated intracellular calcium concentration triggers a series of intracellular biochemical events that
ultimately result in an increase in the force of the myocardial contraction or a positive inotropic effect.

In higher doses they also in higher doses they also have an antiarrhythmic effect by prolonging the refractory period of the AV node (Atrioventricular node), reducing the number of impulses reaching the ventricles. This is used in the treatment of atrial fibrillation, atrial flutter and paroxysmal tachycardia. [111]

3. Flavonoids
Flavonoids are important group of polyphenols widely distributed among the plant flora. Structurally, they are made of more than one benzene ring in its structure and numerous reports support their use as antioxidants or free radical scavengers. The compounds are derived from parent compounds known as flavans. Over four thousand flavonoids are known to exist and some of them are pigments in higher plants. Quercetin, kaempferol and quercitin are common flavonoids present in nearly 70% of plants. Other group of flavonoids include flavones, dihydroflavans, flavans, flavonols, anthocyanidins, proanthocyanidins, catechins and catechin and leucoanthocyanidins [109].

![Basic structures of some pharmacologically important plant derived flavonoids.](image)

Fig: Basic structures of some pharmacologically important plant derived flavonoids.

Biological importance of kaempferol:
Kaempferol can inhibit VEGF production and suppress ovarian cancer cell metastasis in vitro [112]. Kaempferol has been shown to reduce growth in pro-myelocytic leukemia cells through altering the cell cycle [113]. Kaempferol containing foods is not significantly associated with decreased bladder cancer, prostate cancer, or colorectal cancer risk. Consumption of kaempferol-containing foods was associated with a reduced gastric cancer risk” [114]. Consumption of three flavonoids (kaempferol, quercetin, and myricetin) correlated with a lower risk of pancreatic cancer among current smokers, but not non-smokers or ex-smokers [115]. 6-methoxykaempferol-3-O-β-D-glucobioside was shown to have significant inhibitory activity of aldose reductase, which plays an important role in diabetic complications [116]. Kaempferol has been shown to inhibit or decrease the activity of enzymes that participate in viral infection such as reverse transcriptase, viral proteases and neuraminidase [114].

Biological importance of Myricetin:
Myricetin has been seen to demonstrate antiviral activity against a number of viruses including Moloney murine leukemia virus, Rauscher murine leukemia virus, and the human immunodeficiency virus. Its effects against the proliferation of viruses is thought to be a consequence of myricetin’s ability to inhibit the proper functioning of reverse transcriptase. Myricetin was identified as a competitive inhibitor of the reverse transcriptase of Rauscher murine leukemia virus and a partial competitor with respect to the human immunodeficiency virus [117]. Myricetin may prevent oxidative stress-induced platelet activation/aggregation. Thus, consumption of antioxidants may serve an anti-thrombotic function. In addition to offering protection by neutralizing peroxide radicals and effecting thrombixone production via the PTGS1 pathway, polyphenols such as myricetin may target other platelet activation pathways, limiting fibrinogen’s ability to bind platelet surface receptors [118]. It has also been shown that myricetin is effective in protecting neurons against oxidative stressors. Researchers have shown that PC12 cells treated with hydrogen peroxide (H2O2) as an oxidative stress or experience cell death due to apoptosis. When treated with myricetin, these oxidatively stressed cells displayed statistically significant increased cell survival [119]. It has also been shown that myricetin can itself act as an agent of mutagenicity. Myricetin can produce frameshift mutations in the genomes of particular strains of Salmonella typhimurium. In general, biochemical structural studies have shown that flavonoid structures can tautomerize in biological systems to become active mutagens [117].

4. Phenolics
Phenolics, phenols or polyphenolics (or polyphenol extracts) are chemical components that occur ubiquitously as natural colour pigments responsible for the colour of fruits of plants. Phenolics in plants are mostly synthesized from phenylalanine via the action of phenylalanine ammonia lyase (PAL). They are very important to plants and have multiple functions. The most important role may be in plant defence against pathogens and herbivore predators, and thus are applied in the control of human pathogenic infections. They are classified into (i) phenolic acids and (ii) flavonoid polyphenolics (flavanones, flavones, xanthones and catechins) and (ii) non-flavonoid polyphenolics. Caffeic acid is regarded as the most common of phenolic compounds distributed in the plant flora followed by chlorogenic acid known to cause allergic dermatitis among humans [109].
Biological importance of caffeic acid:
Caffeic acid has a variety of potential pharmacological effects, inhibitory effect of caffeic acid on cancer cell proliferation by oxidative mechanism in human HT-1080 fibrosarcoma cell line has recently been established [120]. Caffeic acid is an antioxidant in vitro and also in vivo [121]. Caffeic acid also shows immunomodulatory and anti-inflammatory activity. Caffeic acid outperformed the other antioxidants, reducing aflatoxin production by more than 95 percent. The studies are shown that oxidative stress that would enhance Aspergillus flavus aflatoxin production can be prevented by caffeic acid. This opens the door to using natural fungicide methods by supplementing trees with antioxidants [122].

Studies of the carcinogenicity of caffeic acid have mixed results. Some studies have shown that it inhibits carcinogenesis, and other experiments show carcinogenic effects. Oral administration of high doses of caffeic acid in rats has caused stomach papillomas [123]. In the same study, high doses of combined antioxidants, including caffeic acid, showed a significant decrease in growth of colon tumors in those same rats. Caffeic acid is listed under some Hazard Data sheets as a potential carcinogen, as has been listed by the International Agency for Research on Cancer as a Group 2B carcinogen ("possibly carcinogenic to humans") [123].

Biological importance of chlorogenic acid:
Chlorogenic acid is reported to be a chemical sensitizer responsible for human respiratory allergy to certain types of plant materials [124]. It could be involved in the laxative effect observed in prunes [125]. A study showed that chlorogenic acid may have weak psychostimulant effects in mice. Another study showed chlorogenic acid to have a protective effect in neuroinflammatory conditions on dopaminergic neurons. The DNA damage 8-OH-dG is carcinogenic. In a rat model leading to tongue cancer, in which the oxygen radical forming carcinogen 4-NQO was added to drinking water, 8-OH-dG increased with carcinogen treatment. However, adding chlorogenic acid to the rat diet brought the 8-OH-dG level back to normal [126].

5. Tannins
These are widely distributed in plant flora. They are phenolic compounds of high molecular weight. Tannins are soluble in water and alcohol and are found in the root, bark, stem and outer layers of plant tissue. Tannins have a characteristic feature to tan, i.e. to convert things into leather. They are acidic in reaction and the acidic reaction is attributed to the presence of phenolics or carboxylic group. They form complexes with proteins, carbohydrates, gelatin and alkaloids. Tannins are divided into hydrolysable tannins and condensed tannins. Hydrolysable tannins, upon hydrolysis, produce gallic acid and ellagic acid and depending on the type of acid produced, the hydrolysable tannins are called gallotannins or egalitannins. On heating, they form pyrogallic acid. Tannins are used as antiseptic and this activity is due to presence of the phenolic group [109].
Structures of some pharmacologically important plant derived tannins

Biological importance of gallic acid:
Gallic acid is commonly used in the pharmaceutical industry [127]. It is used as a standard for determining the phenolic content of various analytes by the Folin-Ciocalteau assay; results are reported in gallic acid equivalents. Gallic acid can also be used as a starting material in the synthesis of the psychedelic alkaloid mescaline [128]. It is a weak carbonic anhydrase inhibitor [129]. In basic research, gallic acid extracted from grape seeds has been shown to inhibit the formation of amyloid fibrils, one of the potential causes of Alzheimer’s disease and Parkinson’s disease [130]. One study indicated that gallic acid has this effect on amyloid protein formation by modifying the properties of alpha-synuclein, a protein associated with the onset of neurodegenerative diseases [131].

6. Terpenes
Terpenes are among the most widespread and chemically diverse groups of natural products. They are flammable unsaturated hydrocarbons, existing in liquid form commonly found in essential oils, resins or oleoresins [99]. Terpenoids include hydrocarbons of plant origin of general formula (C5H8)n and are classified as mono-, di-, tri- and sesquiterpenoids depending on the number of carbon atoms. Examples of commonly important monoterpenes include terpinen-4-ol, thujone, camphor, eugenol and menthol. Diterpenes (C20) are classically considered to be resins and taxol, the anticancer agent, is the common example. The triterpenes (C30) include steroids, sterols, and cardiac glycosides with anti-inflammatory, sedative, insecticidal or cytotoxic activity. Common triterpenes: amyrins, ursolic acid and oleanic acid sesquiterpene (C15) like monoterpenes, are major components of many essential oils. The sesquiterpene acts as irritants when applied externally and when consumed internally their action resembles that of gastrointestinal tract irritant. A number of sesquiterpene lactones have been isolated and broadly they have antimicrobial (particularly antiprotozoal) and neurotoxic action. The sesquiterpene lactone, palasin, isolated from Butea monosperma has anthelmintic activity, inhibits glucose uptake and depletes the glycogen content in Ascaridia galli [132].

Fig: Basic structures of some pharmacologically important plant derived terpenes

Biological importance of limonene:
Limonene is common in cosmetic products. As the main odor constituent of citrus (plant family Rutaceae), d-limonene is used in food manufacturing and some medicines, e.g. as a flavoring to mask the bitter taste of alkaloids, and as a fragrance in perfumery, aftershave lotions, bath products and other such products that include fragrance. It is also used as botanical insecticide (EPA, 1994), the d-enantiomer is most active as an insecticide. It is added to cleaning products such as hand cleansers to give a lemon-orange fragrance and because of its ability to dissolve oils. In contrast, l-limonene has a piny, turpentine-like odor. In natural and alternative medicine, d-limonene is marketed to relieve gastrointestinal reflux disease and heartburn [133]. Limonene is increasingly being used as a solvent for cleaning purposes, such as the removal of oil from machine parts, as it is produced from a renewable source. It is used as a paint stripper and is also useful as a fragrant alternative to turpentine. Limonene is also used as a solvent in some model airplane glues and as a constituent in some paints. All-natural commercial air fresheners, with air propellants, containing limonene are used by philatelists to remove self-adhesive postage stamps from envelope paper [134]. Limonene is also finding increased use as a solvent for filament-fused 3D printing. Printers can print the plastic of choice for the model, but erect supports and binders from HIPS, a polystyrene plastic that is easily solvable in limonene. As it is combustible, limonene has also been considered as a biofuel [135].

7. Anthraquinones
These are derivatives of phenolic and glycosidic compounds. They are solely derived from anthracene giving variable oxidized derivatives such as anthrones and anthranols [136] [99]. Other derivatives such as chrysophanol, aloe-emodin, rhein, salinos, poramide, luteolin and emodin have in common a double hydroxylation at positions C-1 and C-8. To test for free anthraquinones, powdered plant material is mixed with organic solvent and filtered, and an aqueous base, e.g. NaOH or NH4OH solution, is added to it. Apink or violet color in the base layer indicates the presence of anthraquinones in the plant sample [94].

Fig: Basic structures of some pharmacologically important plant derived anthraquinones.

Biological importance of mitoxantrone:
Mitoxantrone is used in the treatment of certain types of cancer, mostly metastatic breast cancer, acute myeloid leukemia, and non-Hodgkin’s lymphoma [137]. The combination of mitoxantrone and prednisone is approved as a second-line treatment for metastatic hormone-refractory prostate cancer. Until recently this combination has been the first line of treatment; however, a combination of docetaxel and prednisone has been shown to improve survival rates and lengthen the disease-free period [138]. Mitoxantrone is also used to treat multiple sclerosis (MS), most notably the subset of the disease, known as secondary-progressive MS. As no cure for multiple sclerosis exists yet, it must be understood mitoxantrone will not cure the disease, but rather is effective in slowing the progression of secondary-
progressive MS and extending the time between relapses in both relapsing-remitting MS and progressive-relapsing MS [139].

8. Essential oils

Essential oils are the odorous and volatile products of various plant and animal species. Essential oils have a tendency evaporate on exposure to air even at ambient conditions and are therefore also referred to as volatile oils or ethereal oils. They mostly contribute to the odoriferous constituents or ‘essences’ of the aromatic plants that are used abundantly in enhancing the aroma of some spices [132].

Essential oils are either secreted either directly by the plant protoplasm or by the hydrolysis of some glycosides and structures such as directy. Plant structures associated with the secretion of essential oils include: Glandular hairs, Oil tubes, modified parenchymal cells, Schizogenous or lysigenous passages. Essential oils have been associated with different plant parts including leaves, stems, flowers, roots or rhizomes. Chemically, a single volatile oil comprises of more than 200 different chemical components, and mostly the trace constituents are solely responsible for attributing its characteristic flavour and odour [99].

![Image](https://example.com/image.png)

Fig: Basic structures of some pharmacologically important plant derived essential oils

Biological importance of essential oils:

Medicinal use of essential oils is seen as pseudoscience in the healthcare community [140]. Essential oils retain considerable popular use among advocates of alternative medicine. Studies have shown that certain essential oils may have the ability to prevent the transmission of some drug-resistant strains of pathogen, specifically Staphylococcus, Streptococcus and Candida [141]. Taken by mouth, many essential oils can be dangerous in high concentrations. Typical effects begin with a burning feeling, followed by salivation. In the stomach, the effect is carminative, relaxing the gastric sphincter and encouraging eructation (belching). Further down the gut, the effect typically is antispasmodic [142]. Typical ingredients for such applications include eucalyptus oils, menthol, capsaicin, anise and camphor [143]. Some essential oils, such as those of juniper and agathosma, are valued for their diuretic effects [144]. With relatively recent concerns about the overuse of antibacterial agents [145]. Many essential oils affect the skin and mucous membranes in ways that are valuable or harmful. Many essential oils, particularly tea tree oil, may cause acontact dermatitis [146]. They are used in antiseptics and liniments in particular. Typically, they produce rubefacient irritation at first and then counterirritant numbness. Turpentine oil and camphor are two typical examples of oils that cause such effects. Menthol and some others produce a feeling of cold followed by a sense of burning. This is caused by its effect on heat-sensing nerve endings. Some essential oils, such as clove oil or eugenol, were popular for many hundred years in dentistry as antiseptics and local anaesthetics. Thymol is well known for its antiseptic effects [147].

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