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Review article

Food from plants with antiarthritic properties

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Abstract

Arthritis is a systemic inflammatory disease, affecting mainly joints. There are 2 major types of arthritis, namely; rheumatoid arthritis (RA) and osteoarthritis (OA). RA is a chronic multisystem disease, affecting usually peripheral joints and characterized by hyper-activity of certain immune reactions, persistent synovitis with diffuse proliferation and, in most of the cases, deposition of auto-antibodies to immunoglobulins (rheumatoid factor). OA, the most common type of arthritis**,** is a failure of joint protective mechanism or failure to repair joint injury in the elderly. In the case of severe arthritis, conventional modern medicine is devoid of a satisfactory treatment. The available therapies for arthritis are aimed at reducing the symptoms (pain, inflammation, damage to articular structure, *etc*.). Nonsteroidal anti-inflammatory drugs (NSAIDs) and simple analgesics are used to treat arthritis. The major side effect of NSAIDs is gastro-duodenal ulceration. Immune suppressive and cytotoxic drugs in use to treat RA may ameliorate the disease process in some patients. But they cause a variety of toxic side effects. In traditional medicine, numerous medicinal plants and their polyherbal formulation as well as medicinal foods are used to treat RA and OA. Nutraceutical is used to describe an ingredient of diet including isolated compound or any product derived from food sources that provides extra health benefits in addition to the basic nutritional value found in foods. Arthritis can be delayed, controlled and/or prevented with the dietary supplements, containing antiarthritic plant foods (nutraceuticals). Antiarthritic plant foods, when consumed regularly to the optimum level, could be extremely safe and effective without the adverse effects of currently used NSAIDs and immune-suppressors. Antiarthritic foods or drinks include the leaf extract of *Camellia sinensis*, inner bark of *Cinnamomum verum* (spice), leaves and seeds of *Coriander sativum*, rhizome of *Curcuma longa* (spice and an ingrident of many dishes), carrot (tuberous root of *Daucus carota*), ripe fruit peel and unripe fruit of mango (*Mangifera indica*), fruits of *Piper nigrum* (king of spices) and *Piper longum*, fruit of *Punica granatum*, black berry or black plum (*Syzygium cumini* fruit), seeds of *Trigonella foenum-graecum* (spice and an ingredient of many dishes), and rhizome of *Zingiber officinale*. Since arthritis condition exhibits inflammation of joints, pain, oxidatiove stress and hyperimmune reactions (particularly in the case of rheumatoid arthritis), plant food with high levels of one or more of these properties could ameliorate the symptoms of arthritis. Other pharmacological properties of these food stuffs are to be considered for their proper use as food medicines / nutraceuticals. Pure chemical entity nutraceuticals with antiarthritis properties include chlorophyll-a and its degradation products, curcumin, epicatechin, mangiferin, quercetin and β-sitosterol. These compounds (nutraceuticals) or food stuffs containing these compounds (also known as nutraceuticals) can be judiciously used, considering their mechanisms of action, if known. The mechanisms of action of some of the nutraceuticals mentioned above are known. For example, the anti-inflammatory mechanism of curcumin includes inhibition of cyclo-oxygenases and lipoxygenases; chlorophyll-a and its degradation products exhibit antiarthritis action, primarily by the inhibition of TNF-α production. Further, studies are required to determine the amount (dose) and combinations of plant foods to be consumed for better efficacy against RA and OA.

Key words : Arthritis, antiarthritic nutraceuticals, pepper, ginger, chlorophyll-a, curcumin, mangiferin, cinnamon

1. Introduction

Arthritis is a systemic inflammatory disease, affecting mainly joints. There are 2 major types of arthritis, namely; rheumatoid arthritis and osteoarthritis. Gout is also a type of inflammatory disease, caused by the pathogenic deposition of uric acid crystals in joints and tissues. Conventional modern medicine is devoid of a satisfactory treatment to severe cases of arthritis. To a large extent, these diseases are treated symptomatically and the drugs used in the treatment have varying levels of toxic side effects. In traditional

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medicines, several herbal drugs are used to treat these diseases. However, their efficacy and safety are not clear. Herbal drugs are promising for the development of effective and safe drugs against arthritis. In the recent past, a few reviews have appeared on this topic (Arya *et al.*, 2011; Kaur *et al.*, 2012; Singh *et al.*, 2011; Srikanth *et al.*, 2012; Subramoniam *et al.*, 2013). There are certain plant foods with antiarthritis and / or promising anti-inflammatory and antioxidant properties. These plant-foods could be very safe when used judiciously. This review focuses on commonly used plant foods including spices as therapeutic agents for controlling or preventing arthritis.

2. Arthritis and its treatment

Rheumatoid arthritis (RA): RA is a chronic multisystem disease, characterized by hyperactivity of certain immune reactions, persistent synovitis with diffuse proliferation and, in most of the cases, deposition of auto-antibodies to immunoglobulins known as rheumatoid factor (RF). In severe cases, the synovial inflammation leads to articular cartilage damage, bone erosion and subsequent changes in joint integrity. Usually peripheral joints are involved. The prevalence of RA is about 0.8 %; women are affected more often than men. The prevalence increases with age and in most cases, genetics has a role in the disease susceptibility. However, factors other than genetics such as environmental factors have roles in the incidence and severity of RA (Lipsky, 2008).

It is believed that RA is caused by the adverse response of the body to an infectious agent in genetically susceptible individual. Microvascular injury and an increase in the number of synovial lining cells are the initial changes, observed in synovitis in RA. Then, a perivascular infiltration with mononuclear cells occurs. As the disease-process continues, the synovium becomes edematous and protrudes into the joint cavity. The changes include hyperplasia, and hypertrophy of the synovial lining cells, micro-vascular injury, thrombosis, and neo-vascularization. When the disease progresses, periarticular soft tissue edema also appears (Lipsky, 2008).

The synovitis is also characterized by the infiltration of B cells and antibody producing plasma cells. Polyclonal immunoglobulins as well as autoantibody to immunoglobulins are produced in the synovial tissue. Treatment with monoclonal antibody to B cell marker, CD20 causes a decline in B-lymphocytes, inflammation and serum rheumatoid factor (RF). The synovial fibroblasts are activated to produce collagenase, cathepsins, *etc.*, that degrade components of the articular matrix. Osteoclasts are also prominent at sites of bone erosion.

A number of cytokines and chemokines are secreted in the synovium by activated T cells, macrophages and fibroblasts. These products may account for many of the pathological and clinical manifestations of RA. Thus, it appears that the propagation of RA is an immune system mediated event. Experimental evidence suggests that the inflammatory process is driven by the CD4+ T cells infiltrating the synovium. Macrophages are activated to produce proinflammatory cytokines IL-1 and tumor necrosis factor-α (TNF-α). A large amount of reactive oxygen species (ROS) is produced locally in the synovium. The exudative synovial fluid contains more poly-morphonuclear leucocytes (PMNLs) than monocytes. PMNLs can take up immune complexes including autoimmune complexes with the resultant production of ROS and other inflammatory mediators. The cartilage destruction occurs to a large extent in juxtaposition to the inflamed synovium or pannus that cover the articular cartilage. The cytokines, TNF-α and IL-1 mainly produced by macrophages, stimulate the cells of the pannus (fibroblasts, chondrocytes and small blood vessels) to produce collagenase and other proteases that locally degrade cartilage and inhibit synthesis of new matrix proteins. Involvement of cytokines, IL-17 and IL-18 in the pathogenisis of chronic rheumatoid arthritis has been suggested (Lubberts *et al.*, 2001; Gracie *et al.*, 1999). These cytokines may contribute to the activation of osteoclasts that accumulate at the site of bone resorption (Lipsky, 2008). Systemic manifestations of RA include malaise, fatigue and elevated levels of serum acute phase reactance. Further, rheumatoid nodules may develop in 20-30 % of patients. Osteoporosis, secondary to rheumatoid-involvement, is common among the patients. The symptoms can be ameliorated with monoclonal antibody to TNF-α.

Laboratory findings such as presence of RF are useful to confirm a diagnosis with a suggestive clinical presentation. The ESR is also generally increased in patients with active RA. Disease activity may be correlated with elevated levels of ceruloplasmin, C-reactive proteins, *etc*. Synovial fluid in inflammatory arthritis is usually turbid with reduced viscosity and increased protein content with the predominance of PMNLs. Progression of the disease, systemic involvement and symptoms vary widely among patients. The typical features of RA are bilateral symmetric inflammatory poly-arthritis involving small and large joints in both upper and lower extremities with sparing of axial skeleton except the cervical spine. Other symptoms which substantiate or confirm the typical picture are morning stiffness, subcutaneous nodules, juxta-articular bone demineralization and erosion (radiographic findings).

Osteoarthritis (AO): OA is a joint failure often initiated by joint injury. The pathological changes are hyaline articular cartilage loss, increased thickness and hardening of the subchondral boney plate, outgrowth of osteophytes at the joint margin, stretching of the articular capsule and mild synovitis in many affected joints and weakness of muscles bridging (Felson, 2008). OA is the most common type of arthritis with high rate of disability and high prevalence in the elderly. AO is a failure of joint protective mechanism or failure to repair joint injury in the elderly. The symptoms are pain and disability; bursitis occurs commonly around knee and hip. Likely sources of pain include effusions, marrow edema and synovial inflammation. Stiffness for a short time (less than 30 min in the morning) of the affected joint may be prominent (Lipsky, 2008). In OA, synovitis is mild and not accompanied by conspicuous proliferation of cells. The hyper activity of certain immune reactions occurring in RA are absent in AO and RF is not present.

The disease is heritable in a majority of cases; but its heritability varies by joint. OA commonly affects the cervical and lumbosacral joint, hip, knee and first metatarsal phalangeal joint. Usually spared are the wrist, elbow and ankle. Symptomatic OA of the knee is the most prevalent which occurs about 12 % of Americans above 60 years of age; this is followed by hip AO and hand OA. OA is more common in women than in man. Age is the most potent risk factor for AO and the joint vulnerability increases with age due to weakening of joint protective mechanisms against loading and minor injuries.

2.1 Treatment for arthritis

The available therapies for rheumatoid arthritis (RA) are not curative and are aimed at reducing the symptoms (pain, inflammation, damage to articular structure, *etc*.). Some of the therapies employed are directed at non-specific suppression of the inflammatory or immunological process (Lipsky, 2008).

Non steroidal anti-inflammatory drugs (NSAIDs) and simple analgesics currently used include ibuprofen, nabumetone, naproxen, salsalate, piroxican, ketorolak and ketoprofen. Although these drugs reduce inflammation and pain, they exert minimal effects on the progression of the disease. Further, the major side effect of NSAIDs is gastro-duodenal ulceration. Most of the NSAIDs inhibit both COX-1 and COX-2. New, selective inhibitors of COX-2 exhibit less gastro-duodenal ulcers compared to NSAIDs. However, COX-2 inhibition is associated with the risk of cardiovascular events. Low dose of oral glucocorticoids are used as additional second line of therapy to suppress signs and symptoms of inflammation. Intra-articular injection of glucocorticoids can often provide symptomatic relief when systemic therapy has failed to resolve inflammation.

Disease modifying drugs (DMDs) for RA are thought to modify the inflammatory component of RA. These drugs include methotrexate, sulfasalazine, hydroxychloroquine, gold salts and D-penicillamine. Most of them exert minimal direct anti-inflammatory and analgesic effects and, therefore, NSAID may be continued with them. Methotrexate has emerged as the DMD of choice especially in individuals with risk factor for the development of bone erosions or persistent synovitis. Toxicity of DMDs includes gastrointestinal upset, oral ulceration, liver function abnormalities and drug induced pneumonitis. TNF-α neutralizing agents (infliximab, etanercept and adalimumab), IL-1 neutralizing agents (anakinra), drugs that deplete B cells (rituximab) and those that interfere with T cell activation improve signs and symptoms of RA and decrease disability. Out of these agents, TNF-α neutralizing agents are better in efficacy. The major side effects of these agents include potential for an increase in the risk of serious infections such as tuberculosis; increase in the risk of lymphoma and other malignancies.

Immune suppressive and cytotoxic drugs in use include leflunomide, cyclosporine, azathioprine and cyclophosphamide. These may ameliorate the disease process in some patients. But they cause a variety of toxic side effects. For example, leflunomide alters liver function enzymes (Lipsky, 2008).

In conventional medicine, non-pharmacological approaches are the major therapies for OA; pharmacotherapy serves an important adjunctive role in OA treatment. The simplest effective treatment for many patients is to avoid activities that precipitate pain. In the case of obese people, considerable weight loss may lessen symptoms of knee and hip AO. Exercises are likely to be effective if they train muscles for the activities a person performs daily. Mild and appropriate exercise may improve the functioning of muscles surrounding the joint (Lipsky, 2008). Correcting mal-alignment either surgically or with bracing can relieve pain in patients whose knees are mal-aligned. In patients with knee OA, acupuncture produces modest pain relief compared to placebo needle. Paracetamol is the initial analgesic of choice for patients with AO in knees, hip or hands. However, NSAIDs are the most popular drugs to treat AO pain. COX-2 inhibitors are also used. Intra-articular glucocorticoid injections may be effective in ameliorating pain and synovial inflammation. When medical therapies have failed, in severe cases of knee and hip OA, joint arthoplasty is indicated.

In traditional medicine including different traditional systems of medicine such as Ayurveda, numerous medicinal plants and their polyherbal formulations are used to treat RA and OA (Subramoniam *et al.*, 2013).

3. Plant nutraceuticals (Bioactive plant foods)

If ingredients of diet or edible items have medicinal values, they are known as medicinal food or functional food or bioactive food. Bioactive molecules present in functional food are nutraceuticals; functional foods are also considered as nutraceuticals or food-medicines (Subramoniam, 2016a). The term nutraceutical was originally defined by Dr. Stephen L. DeFelice, Founder and Chairman of the Foundation of Innovation Medicine, Crawford, New Jersey in 1979 (Brower, 1998). Since the term was coined by Dr. DeFelice, its meaning has been modified by Health Canada which defines nutraceutical as “a product isolated or purified from foods, and generally sold in medicinal forms and demonstrated to have a physiological benefit or provide protection against chronic diseases”. This definition is not accepted by all scientists and in most of the countries. Nutraceutical is used to describe an ingredient of diet including isolated compound or any product derived from food sources that provides extra health benefits in addition to the basic nutritional value found in foods. The definition of nutraceuticals that appears in the latest edition of the Merriam-Webster Dictionary is as follows: A food stuff (as a fortified food or a dietary supplement) that provides health benefits.

A dietary supplement is a product taken by mouth that contains a dietary ingredient or ingredients intended to supplement the diet. The dietary ingredients may include vitamins, minerals, amino acids and bioactive phytochemicals from edible parts of plants. Dietary supplements contain nutrients derived from food products that are generally concentrated in many forms such as liquids, powders, tablets, capsules, *etc*. If a dietary supplement contains bioactive compound or compounds with health benefits, it is also nutraceuticals. For example, garlic extract is sold as dietary supplement to lower blood lipids.

Functional foods are also nutraceuticals. Health Canada defines functional foods as ordinary food that has components or ingredients added to give it a specific medical or physiological benefit, other than a purely nutritional effect. Normally, functional foods are designed to allow consumers to eat enriched foods close to their natural state. In Japan, all functional foods must meet three established requirements: foods should be (i) present in their naturally-occurring form, rather than a capsule, tablet, or powder; (ii) consumed in the diet as often as daily; and (iii) should regulate a biological process in hopes of preventing or controlling disease (Hardy, 2000).

Food materials (ingredients of diet) with medicinal properties are known as medicinal food. These are also nutraceuticals with bioactive molecules. However, medicinal foods are not available as an over-the-counter product to consumers in USA (Brower, 1998). The FDA considers medical foods to be formulated, to be consumed or administered internally under the supervision of a physician, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements,

on the basis of recognized scientific principles, are established by medical evaluation (Hardy, 2000). This applies, when medicinal foods are designed to meet certain nutritional requirements for people, diagnosed with specific illnesses. Nutraceuticals and food supplements that do not meet these requirements are not classified as medicinal foods in USA. But, these demarcations are not applied in all countries.

Plant based nutraceuticals are plant products with nutritional and medicinal values. In other words, these are food (ingredients of diet) with pharmaceutical properties (bioactivities). Nutraceuticals have health benefits when consumed to the optimum levels. The preference for the discovery and production of nutraceuticals over pharmaceuticals is well seen in pharmaceutical and biotech companies. One of the reasons for the same is that diet and dietary ingredients with medicinal properties are likely to be very safe. Vegetables (like bitter gourd), fruits (like grapes and papaya), rice bran, gooseberry, and spices (such as turmeric and garlic), are examples of nutraceuticals. These ingredients of food have biologically active molecules. For example, curcumin from turmeric have antioxidant, antidiabetic, anti-inflammatory and cancer preventive properties. Similarly, sulfur compounds in garlic extract have hypolipidemic property. Grapes and pea nuts contain, among other things, pharmacologically active resveratrol. Herbal drugs which are not edible (not ingredients of diet) are not nutraceuticals. Plant foods are edible parts (as such or after cooking) of plants accepted by any community through custom, habit and tradition as appropriate, desirable food or ingredients of diet. Generally, food items provide nutrients to the body without any short or long term adverse effects to health and well being.

Certain pharmacy and biotech companies erroneously extended the term nutraceutical even to isolated compounds from wild plants which are not edible (Kamboj, 2000). For example, docosohexaenoic acid, a cardiovascular stimulant from algae was marketed as nutraceuticals. Many herbal preparations are being marked as nutraceuticals without following the minimum standards, laid down by WHO to herbal drugs (WHO, 1991). This is a dangerous trend considering human health. The Dietary Supplement Health Education Act passed by USA in 1994 permits to make unprecedented claims about the health benefits of food or dietary supplements. In view of this, unfortunately, many herbal remedies and isolated compounds are marketed as nutraceuticals by some of the pharmacy companies. The regulatory agents should stop this dangerous trend as was done by US-FDA by banning the so called dietary supplement cholestin (lavastatin).

Farmaceuticals refer to medically valuable compounds, produced from modified agricultural crops or animals (usually produced through biotechnological intervention). Proponents believe that using crops and possibly even animals as pharmaceutical factories could be much more cost effective than conventional methods. The term farmaceuticals is more frequently associated in agricultural circles with medical applications of genetically engineered crops or animals. If a non-nutraceutical drug is produced in an edible plant, it is not a nutraceutical.

4. Edible plants with antiarthritic properties

Most of the plants with antiarthritis activities in their edible parts are given below along with their other pharmacological properties and so on. Since arthritic condition exhibits inflammation, pain, oxidative stress, *etc*., plants with high levels of these properties along with traditional use to treat arthritis are also included under antiarthritic plants.

1. *Camellia sinensis* (Linn.) Kuntze, Theaceae, tea plant

C. sinensis is commonly known as tea plant. The leaves are used worldwide for the preparation of tea. It is considered as the native of Southern Yunnan and Upper Indo-China and now it is cultivated over a circular range of tropical and subtropical regions.

Plant description: *C. sinensis* is an evergreen tree, growing to a height of 9-15 m; leaves simple, alternate, elliptic, obovate and lanceolate with serrate margin; flowers may be either solitary or may occur in clusters of 2-4 and are white and fragrant. Seeds 1-3, produced in brownish green capsule.

Traditional medicinal uses: It is analgesic, astringent, demulcent, diuretic, lactogogue and narcotic and is used in inflammation, abdominal disorders, fever, strangury, fatigue and hemicrania, pain of heart, eye troubles, *etc* (Subramoniam, 2016a).

Antiarthritic activities: One of the polyphenols, epigallocatechins, present in tea is a potent antioxidant (Kaur *et al*., 2012). Green tea protected against ethanol-induced lipid peroxidation in rat organs. Tea leaves has promising anti-inflammatory and hypolipidemic activities (Subramoniam, 2016a).

In collagen-induced arthritic rats, green tea markedly reduced inflammation and inflammatory cytokines (TNF-α and γ-interferon and COX-2). The levels of total IgG antibodies and collagen specific antibodies were reduced by green tea (Kaur *et al*., 2012; Ahmed, 2010). Recent findings suggest that black tea extract has antiarthritic activity in both experimental and clinical study. Black tea water extract showed antiarthritic activity in Freund's complete adjuvant induced-arthritic rats with an associated decrease in the serum levels of PGE2, TNFα, IL-1β and IL-6 (Datta *et al*., 2012).

Other activities: *C. sinensis* is a chemopreventive agent. Inhibition of lung carcinogenesis by oral administration of green tea is likely to be mediated by inhibition of angiogenesis and induction of apoptosis in A/J mice. Green tea polyphenols exhibited anti-mutagenic activity against tobacco induced mutagenicity.

C. sinensis (black tea) showed antihyperglycemic effect in rat (Gomes *et al*., 1995). Tea showed *in vitro* insulin-enhancing activity and the predominant active ingredient is epigallocatechin gallate. The water extract of leaves was found to be effective to reduce most of the diabetes associated abnormalities in streptozotocin diabetic rats (Islam, 2011). The water extract of the leaves (200 mg/kg), containing catechins reduced hyperglycemia-induced renal oxidative stress and inflammation in streptozotocin-induced male diabetic rats (Kumar *et al*., 2012). In an *in vitro* study, catechin promoted adipocyte differentiation in human bone marrow mesenchymal stem cells through PPARγ activation (Wang *et al*. 2014).

Phytochemicals: Reported phytochemicals include epigallocatechin gallate (the major flavonoid of green tea), polysaccharide conjugates, purine alkaloids, theaflavins, thearubigins caffeine, theophylline, xanthine, hypoxanthine, dextrins, kaempferol, quercetin, barringtogenol, cinnamic acid, angelic acid, glucuronic acid, sapogenol, putrescine, theanine, typhasterol, teasterol, umbelliferone, scopoletin and α-spinasterol-β-D-gentiobioside (Subramoniam, 2016a).

2. *Cinnamomum verum* J.S. Presl., syn: *Cinnamomum zylanicum* Nees, *Laurus cinnamomum* L.

Common names for *C. verum* include Cylon cinnamon, true cinnamon and cinnamon. *C. verum* is indigenous to Sri Lanka and southern parts of India. *Cinnamomum cassia* J. Presl, a related species, originated in southern China, and widely cultivated there and elsewhere in southern and eastern Asia. Cinnamon is used as a common spice by different cultures around the world for several centuries. It is obtained from the inner bark of trees from the genus *Cinnamomum*.

Plant description: *C. verum* is a small ever green tree; bark smooth, pale; young parts glabrous except the buds which are finely silky; leaves opposite or subopposite (rarely alternate), hard and coriaceous, 7-18 cm long, ovate or ovate lanceolate, subacute or shortly acuminate, base acute or rounded; petioles 1.3-2.5 cm long, flattened above. Flowers are numerous, in silky pubescent, lax panicles usually longer than the leaves. Perianth 5-6 mm long; tube 2.5 mm long; segments pubescent on both sides, oblong or somewhat obovate, usually obtuse. The fruit is a purple generally about 1 cm drupe containing a single seed. Ceylon cinnamon sticks (quills) have many thin layers and can be easily made into powder (Subramoniam, 2016a).

Traditional medicinal uses: In Ayurvedic medicine, cinnamon is considered a remedy for respiratory, digestive and gynecological ailments. In traditional medicine, it is also used for rheumatism, neuralgia, wounds, diabetes, inflammation of eyes, impotence and leucorrhea (Subramoniam, 2016a).

Antiarthritic activities: The essential oils obtained from the bark and eugenol exhibited powerful antioxidant activity. The dried fruit extracts also exhibited antioxidant activity; water extract was found to be the most active extract (Ranasinghe *et al*., 2013). Phenolic compounds such as hydroxyl cinnamaldehyde and hydroxycinnamic acids present in the cinnamon extract scavenge peroxide radicals and prevent oxidative damages (Faix *et al*., 2009). Cinnamon has anti-inflammatory and analgesic properties also (Ranasinghe *et al*., 2013). Type-A procyanidine polyphenols extracted from cinnamom showed significant anti-inflammatory effect at doses of 4, 8 and 25 mg/kg, p.o. in carrageenan-induced rat paw edema model. Type-A procyanidine polyphenols (8 mg/kg, p.o., daily from day-12 to day-21) treatment in established arthritic rats showed significant reversal of changes induced in adjuvant induced established arthritis with respect to body weight drop (cachexia), ankle diameter, arthritic score and serum C-reactive protein levels. Moreover, type-A procyanidine polyphenols was found to be non-ulcerogenic as compared to untreated arthritic control rats. However, type-A procyanidine polyphenols did not show analgesic effect on arthritis-induced pain as seen in Randall-Selitto assay. In conclusion, type-A procyanidine polyphenols showed disease-modifying potential in animal models of inflammation and arthritis in rats (Vetal *et al*., 2013).

Other activities: The antidiabetes mellitus properties of *C. verum* are reviewd in a book recently (Subramoniam, 2016a). *In vitro* anti-diabetes mellitus activities of *C. verum* include stimulation of cellular glucose uptake by translocation of GLUT4 to the membrane; stimulation of glucose metabolism and glycogen synthesis; inhibition of gluconeogenesis by influencing key regulatory enzymes; inhibition of pancreatic α-amylase and α-glucosidase; and stimulation of insulin release and potentiation of insulin signaling. Cinnamtannin B1 was identified as the potential active compound responsible for these effects. The *in vivo* beneficial effects of *C. zylanicus* include reduction of fasting blood glucose levels in diabetic animals; reduction in the levels of HbA1c and increase in the levels of insulin levels in blood. Methylhydroxychalcone polymer from *Cinnamomum* sp. was found to be an effective mimetic of insulin in 3T3-LI adipocytes. Water-soluble polyphenol type A polymers from cinnamon that increase insulin-dependent *in vitro* glucose metabolism roughly 20-fold and display antioxidant activity were isolated and characterized from *Cinnamomum* sp (Subramoniam, 2016a). Other reported important pharmacological properties of *Cinnamomum* sp. include antimicrobial properties, antiparasitic activities, vasorelaxant activity, hepatoprotective activity, antiulcer activity, antidiarrhoea activity, anti-inflammatory activity and anti-cancer activity (Subramoniam, 2016a). *In vivo* studies on animals showed lack of significant toxic effects on liver, kidney, *etc*. However, there are contradicting reports regarding possible abortive or embryo-toxicity of cinnamon to mice (Subramoniam, 2016a).

Phytochemicals: Cinnamaldehyde is rich in bark whereas eugenol concentration is high in leaf, and camphor level is more in root (Ranasinghe *et al.*, 2013). Three of the main components of the essential oils obtained from the bark of *C. zeylanicum* are trans-cinnamaldehyde, eugenol and linalool, which represent 82.5% of the total composition. One important difference between Chinese cinnamon (*C. cassia*) and Cylon cinnamon is their coumarin (1, 2-benzopyrone) content. The levels of coumarins in Chinease cinnamon appear to be very high and, according to the German Federal Institute for Risk Assessment, pose health risks if consumed regularly in higher quantities. Other reported compounds in *Cinnamomum* sp include rutin, catechin, quercetin, kaempferol and isorhamnetin (Rao and Gan, 2014).

3. *Coriander sativum* L., Apiaceae

Common names of *C. sativum* include coriander, cilantro, Chinese parsley (Eng.), dhanyaka, dhania (Hindi) and yuan sui (Chinese). *C. sativum* is native to the eastern Mediterranean region and southern Europe. The herb is valued for the dry ripe fruits, called coriander seeds. It is cultivated in many parts of the world *(*Nadeem *et al*., 2013). Coriander is grown as a valuable spice crop in India and elsewhere.

Plant description: *C. sativum* is an annual, branched, smooth herb, growing about 30 cm in height. Leaves are pinnately or ternately decompounds; the ultimate segment of the lower leaves is ovate or lanceolate and deeply cut; the upper leaves are more finely dissected into narrow linear segments. Flowers are small white or pinkish purple in compound terminal umbels. Fruits are yellowish brown, globose, 4-5 mm in diameter, ribbed, separating into 2 halves. Seeds are convex-concave, about thrice as broad as they are thick.

Traditional medicinal uses: *C. sativum* has been widely used in traditional medicine for treatment of rheumatoid arthritis and diabetes. In addition, the seeds have been used to treat indigestion, and pain in the joints. Infusion of the fruit is used for dyspepsia; coriander oil is used for flatulence, colic, rheumatism, and neuralgia. Seeds are chewed for halitosis; paste of seeds is applied for headaches; seeds are used in lotions or bruised for poultice in rhuematic pains; decoction of plant in milk is used for bleeding piles; cold infusion of seeds or powder of dried seeds with a little

sugar is used for colic in children (Nadeem *et al.*, 2013; Subramoniam, 2016a**).**

Antiarthritic activities: Coriander seed possesses antiarthritic activity, anti-inflammatory activity, antioxidant activity and hypolipidemic activity (review: Enas, 2010). *C. sativum* hydroalcohol extract produced a dose dependent inhibition of joint swelling as compared to control animals in both, formaldehyde and Complete Freund's adjuvant induced arthritis in rats. Although there was a dose dependent increase in serum TNF-α levels in the extract treated groups as compared to control, the synovial expression of macrophage derived proinflammatory cytokines was found to be lower in the extract treated groups as compared to control. The antiarthritic activity of coriander may be attributed to the modulation of proinflammatory cytokines in the synovium (Nair *et al.*, 2012). Cineole (one of the compounds of essential oil of coriander) and linoleic acid present in coriander possess anti-arthritic properties (Rajeshwari and Andulla, 2011).

Other activities: Hypolipidemic and hypocholesterolemic effects of *C. sativum* (coriander) seeds have been shown in a few studies (Sharma *et al.*, 2013). *C. sativum* seeds showed significant inhibition in hydroxyl methyl glutaryl CoA reductase and plasma lecithin cholesterol acyl transferase activity in hypercholesterolemic rats and enhanced degradation of cholesterol to faecal bile acids and neutral sterols (Dhanapakiam *et al.*, 2008). Coriander has promising anti-diabetes mellitus activity. Coriander incorporated into the diet (62.5 g/kg) and drinking water (2.5 g/l, decoction) reduced hyperglycaemia of streptozotocin-diabetic mice. Water extracts of coriander (1 mg/ml) increased 2-deoxy glucose transport, glucose oxidation and incorporation of glucose into glycogen in isolated murine abdominal muscle. In acute tests, 0.25-10 mg/ml water extract of coriander evoked a stepwise stimulation of insulin secretion from a clonal β-cell line. The effect of extract was potentiated by 16.7 mM-glucose and 10 mM-L-alanine. Insulin secretion by hyperpolarized β-cells (16.7 mM-glucose, 25 mM-KCl) was further enhanced by the presence of extract. Sequential extraction with solvents revealed insulin-releasing activity in hexane and water fractions, indicating a possible cumulative effect of more than one extract constituent. These results demonstrate the presence of antihyperglycaemic, insulin-releasing and insulin-like activity in *C. sativum*. Administration of the ethanol extract (200 and 250 mg/kg, i.p.) exhibited a significant reduction in serum glucose levels (Eidi *et al.*, 2008). *C. sativum* (fruit) reduced plasma glucose, total cholesterol and LDL in obese-hyperlipidemic diabetic rats (Aissaoui *et al.*, 2011). In another study, the water extract of *C. sativam* fruits (250 and 500 mg/kg) decreased blood glucose levels in streptozotocin-induced diabetic rats (Maquvi *et al.*, 2012). The seed is reported to contain compounds with known antidiabetes mellitis properties such as quercetin, rutin, β-sitosterol and chlorogenic acid (Subramoniam, 2016a). In a clinical trial, the hypoglycemic effect of *C. sativam* was investigated in type 2 diabetic patients. The study showed that the high dose of *C. sativum* (4.5 g/day for 14 days), has significant hypoglycemic activity (Waheed *et al.*, 2006).

Other reported pharmacological activities include antibacterial action, immune-stimulant effect, anthelmintic activity, cardio-vascular activity, anxiolytic activity, hepatoprotective activity, diuretic effect and cytotoxicity of essential oils. Coriander seed (water extract) showed protection and an improvement in therapeutic action on pyramidal cells in cerebral cortex against neurodegenerative disorders and Alzheimer' disease induced by aluminum chloride treatment (Enas, 2010). Water extract of fresh coriander seeds showed anti-implantation effect in rats. Further, the extract produced a significant decrease in serum progesterone levels on day-5 of pregnancy which could be responsible for the anti-implantation effect observed **(**Paarakh, 2009).

Phytochemicals: Seeds contain β-sitosterol, D-mannitol, flavonoid glycoside, chlorogenic acid, caffeic acid, rutin, scopoletin, coriandrinonediol, etroselinic acid, oleic acid, linolenic acid, lauric acid, myristic acid, palmitoleic acids, quercetin-3-O-caffeyl glycoside, kaempferol-3-glucoside and octadecenoic acid. Seed oil components include α-pinene, limonene, β-phellandrene, 1, 8-cineole, linalool, borneol, β-caryophyllene, citronellol, geraniol, thymol, linalyl acetate, geranyl acetate, caryophyllene oxide, elemol, methyl heptenone, petroselinic acid. β-sitosterol, triacontane, triacontanol, tricosanol, psoralen, angelicin, coriandrinol, β-sitosterol glucoside, butyl phthalides-neoenidilide, Z-ligustilide, coriandrin, dihydrocoriandrin28, coriandrone A, coriandrone B, and coriandrone C to E have been reported from whole plant. Fruits contain gnaphaloside A, gnaphaloside B, quercetin, isorhamnetin, rutin, and luteolin (Subramoniam, 2016a).

4. *Curcuma longa* L., Zingeberaceae

Common names of *C. longa* include turmeric (Eng.), haridra, haldi, manjal, manja (Indian languages) and so on. It is considered as native of South Asia; cultivated extensively in almost all states of India as well as in the warmer parts of the world, precisely in China and East Indies. The rhizome of this plant is consumed as a spice, food additive and medicine.

Plant description: *C. longa*, a perennial herb and member of the Zingiberaceae (ginger) family, grows to a height of three to five feet and is cultivated extensively in India, China, and other countries with a tropical climate. It has oblong, pointed leaves and funnel-shaped yellow flowers.

Traditional medicinal uses: It is tonic, blood purifier, antiperiodic, stomachic, appetizer, antispasmodic, antiseptic, antacid, carminative, alternative and used in common cold, skin diseases, indolent ulcers, purulent opthalmia, bacterial diseases, arthritis, bone fractures, cough, inflammation, whooping cough, abscesses, conjunctivitis, dysentery, gonorrhoea, jaundice, hepatosis, parturition, pyuria, skin sores, wounds, scabies, burns and vertigo. Turmeric paste mixed with lime and saltpetre is used externally in rheumatism (Subramoniam, 2016a).

Antiarthritic activities: The plant rhizomes have several pharmacological properties which include inhibition of cellular reactive oxygen species generation and anti-inflammatory activity (Subramoniam, 2016a; Labban, 2014). It is a chemopreventive and chemotherapeutic agent in diseases such as inflammatory disorders including arthritis, cancer, diabetes and obesity (Beevers and Huang, 2011). Oral administration of curcumin in instances of acute inflammation was found to be as effective as cortisone or phenylbutazone, and one-half as effective in cases of chronic inflammation. In rats with Freund's adjuvant-induced arthritis, oral administration of turmeric significantly reduced inflammatory swelling compared to controls (Chandra and Gupta, 1972; Arora *et al.*, 1971). In monkeys, curcumin inhibited neutrophil aggregation

associated with inflammation (Srivastava, 1989). The anti-inflammatory properties of *C. longa* may be attributed to its ability to inhibit both biosynthesis of inflammatory prostaglandins from arachidonic acid, and neutrophil function during inflammatory states. Curcumin may also be applied topically to counteract inflammation and irritation associated with inflammatory skin conditions and allergies (Mukhopadhyay *et al*., 1982). Many studies have revealed that curcumin is a highly pleiotropic molecule capable of interacting with numerous molecular targets involved in inflammation (Kohli *et al*., 2005). Cell culture studies, animal experiments and clinical trials indicate that curcumin may have potential as a therapeutic agent in diseases such as inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis (Jurenka, 2009). Turmeric extract containing curcuminoids prevented experimental rheumatoid arthritis (Funk *et al*., 2006).

Crude or refined the turmeric essential oils dramatically inhibited joint swelling (90-100% inhibition) in female rats with streptococcal cell wall-induced arthritis when extracts were administered *via* intraperitoneal injection to maximize uniform delivery. However, this antiarthritic effect was accompanied by significant morbidity and mortality. Oral administration of a 20-fold higher dose the essential oils were nontoxic, but only mildly joint-protective (20% inhibition). These results do not support the isolated use of the essential oils for arthritis treatment but, instead, identify potential safety concerns in vertebrates exposed to the turmeric essential oils (Funk *et al*., 2010).

Other activities: Turmeric's protective effects on the cardiovascular system include lowering cholesterol and triglyceride levels, decreasing susceptibility of low density lipoprotein (LDL) to lipid peroxidation (Ramirez-Tortosa *et al*., 1999) and inhibiting platelet aggregation (Ammon and Wahl, 1991). These effects have been noted even with low doses of turmeric. A study of 18 atherosclerotic rabbits given low-dose (1.6-3.2 mg/kg, daily) turmeric extract demonstrated decreased susceptibility of LDL to lipid peroxidation, in addition to lower plasma cholesterol and triglyceride levels. The higher dose did not decrease lipid peroxidation of LDL, but cholesterol and triglyceride level decreases were noted, although to a lesser degree than with the lower dose (Ramirez-Tortosa *et al*., 1999). The alcohol extract of *C. longa* exerted cholesterol and triglyceride lowering activity (Pachauri and Mukherjee 1970; Purohit and Darakha, 1999). Besides, it has been reported that sodium curcuminate isolated from *C. longa* is an active cholorectic that causes an increase in total excretion of bile salts, bilirubin and cholesterol (Mukherjee, 2003). Oral administeration of curcumin (0.2 %) for 8 weeks to hypercholesterolemic rats resulted in lowering blood cholesterol levels as judged from normalization of erythrocyte membrane fluidity and fragility (Kempaiah and Srinivasan, 2005). Curcumin treatment to human hepatoma cell line HepG2 caused changes in gene expression which are consistent with the proposed hypocholestrolemic effect of curcumin (Peschel *et al*., 2007).

Water-and fat-soluble extracts of turmeric and its curcumin component exhibit strong antioxidant activity, comparable to vitamins C and E5. A study of ischemia in the feline heart demonstrated that curcumin pretreatment decreased ischemia-induced changes in the heart (Dikshit *et al*., 1995). Curcumin enhanced cellular resistance to oxidative damage (Mortellini *et al*., 2008). Other reported activities include antidiabetes mellitus, hypolipidemic activity and antiviral activity. It is recommended for the prevention and control of type 2 diabetes. Active principles such as curcumin, demethoxycurcumin, sesquiterpenoids, bisdemethoxycurcumin, and ar-turmerone, act *via* peroxisome proliferator-activated receptor (PPAR)-gamma ligand-binding activity (Subramoniam, 2016a). Curcumin was found to inhibit PTP1B. The compound improved insulin and leptin sensitivity in the liver of rats; it prevented hypertriglyceridemia and hepatic steatosis in fructose-fed rats (Li *et al*., 2010a). Turmeric volatile oils inhibited α-glucosidase enzymes more effectively than the reference standard drug acarbose. Drying of rhizomes was found to enhance α-glucosidase and α-amylase inhibitory capacities of volatile oils. Ar-turmerone, the major volatile component in the rhizome also showed potent α-glucosidase (IC_{50}: 0.28 μg/ml) and α-amylase (IC_{50}: 24.5 μg/ml) inhibition (Lekshmi *et al*., 2012). Further, curcumin can prevent some of the diabetic complication primarily due to its antioxidant and anti-inflammatory properties (Huang *et al*., 2013; Soetikno *et al*., 2012). Human clinical studies indicate that *C. longa* may have an effect on insulin secretion (Wickenberg *et al*., 2010).

Therapeutic benefits of turmeric have been demonstrated for a variety of gastrointestinal disorders including dyspepsia, peptic ulcer and *Helicobacter pylori* infection. It is beneficial to irritable bowel syndrome also. Turmeric and curcumin isolated from it have potentiality to prevent carcinogenesis and suppress certain types of cancer growth. Curcumin, arturmerone, *etc*., are known to induce apoptotic cell death. However, it can prevent oxidative stress mediated apoptosis due to its antioxidant property. Contraceptive effect of turmeric in male albino rat has been shown (Ashok and Meenakshi, 2004; review: Labban, 2014). Due to its cytotoxic and apoptotis induction potential high concentration could be toxic.

Phytochemicals: Curcumin, essential oil containing d-α-phellandrene, b-terminone, d-sabinene, cineol, borneol, zingiberene, dimethoxy curcumin, bis demethoxy curcumin, turmerones, p-tolylmethyl carbinol, campesterol, stigmasterol, β-sitosterol, cholesterol, monoenoic acid, dienoic acid, 4-hydroxycinnamoyl (feruloyl) methane, bis-(4-hydroxycinnamoyl)methane, bis-demethoxy curcumin (Subramoniam, 2016a).

5. *Daucus carota* L., Apiaceae

Common names of *D. carota* include wild carrot and bird's nest. *D. carota* is grown for its edible root (a common vegetable). The plant is believed to have originated in Europe or the Western Mediterranean; it is naturalized to North America, Australia and so on.

Plant description: *D. carota* is a biennial herb which produces a rosette of 8–12 leaves above ground and a fleshy conical taproot below ground. The plant produces small (2 mm) flowers which are white, red or purple in color. The root can grow to between 5 and 50 cm long and reach 5 cm in diameter. The foliage of the plant can reach a height of 150 cm when in flower.

Traditional medicinal uses: In traditional systems of medicine, *D. carota* has been used as a diuretic and inotropic; it is also used to treat gout, cystitis and lithuria (Patil *et al*., 2012).

Antiarthritic activities: Extract obtained from various parts of the plant possesses analgesic and anti-inflammatory properties (Prochezhian and Ansari, 2000). The ethanol extract of *D. carota* seeds (200 and 400 mg/kg, p.o.) exhibited anti-inflammatory and analgesic activity in carrageenan-,histamine-and serotonin-induced

paw edema (acute inflammation) in rats. Further, the extract showed anti-arthritis activity in formaldehyde-induced arthritis (chronic model) in rats. The acetic acid-induced writhing response and formalin-induced paw licking time in the early and late phases of mice were used to assess analgesic activity. The extract (200 and 400 mg/kg, p.o.) significantly attenuated the writhing responses induced by an intraperitoneal injection of acetic acid in mice and late phase of pain response induced by subplantar injection of formalin in mice (Vasudevan *et al*., 2006). Dietary carrot (10 and 20 % in diet for 6 weeks) exhibited anti-hypercholesterolmic and anti-oxidant activities in hypercholesterolmic rats (Afidy *et al*., 2013)

Other activities: Dietary carrot (10 and 20 % in diet for 6 weeks) lowered blood cholesterol in hypercholesterolmic rats and improved the blood picture and reduced blood glucose level in hypercholesterolemic rats (Afify *et al.*, 2013). In a recent study, falcarinol (polyacetylene) isolated from carrot stimulated glucose uptake in normal and insulin resistant primary porcine myotubes. This effect was attenuated in the presence of indinavir (GLUT4 inhibitor) and wortmannin, (PI3K and MAPK inhibitor) indicating a dependence on GLUT4 activity as well as PI3K and/or p38MAPK activity. Further, falcarinol-stimulated glucose uptake was independent of AMPK activity. Besides, falcarinol enhanced phosphorylation of TBC1D1 suggesting that this compound enhanced translocation of GLUT4 containing vesicles and thereby glucose uptake *via* a TBC1D1-dependent mechanism (Bhattacharya *et al.*, 2014).

Other reported activities of carrot include hepatoprotection, anti-ulcer, antifertility, anticancer and antitumor properties (Patil *et al*., 2012).

Phytochemicals: Phenolic derivatives, tannins and flavonoids are present in the root. Falcarinol (polyacetylene) has also been isolated from carrot.

6. *Mangifera indica* L., Anacardiaceae

Common names of *M. indica* include mango tree, amara, aam, mamaram and mavu. It is a native from tropical Asia. It is cultivated in many tropical and sub tropical regions, southward towards peninsular India for its valued fruits.

Plant description: *M. indica* is a large tree with widely spreading branches. Leaves simple, petiolated, alternate, crowded at the end of the branches, quite entire margin often undulate. Petioles swollen at base; flowers small, yellow, odorous, male and female flowers borne on the same panicle; fruit is a drupe, fleshy with fibres and compressed stone.

Traditional medicinal uses: *M. indica* is astringent, diuretic, parasiticide, apertif, ascaricide, deutrifice, stomachic, taenifuge, vermifuge, laxative, styptic, aphrodisiac, depurative, diaphoretic and antipyretic. It is used in asthma, anasarca, anaemia, cough, diarrhoea, glossitis, hematachezia, hemoptysis, jaudice, hypertension, insomnia, hemiplegia, haemorrhage, leucorrhea, malaria, melaena, opthalmia, piles, rheumatism, rickets, stomatitis, warts, tooth ache, sore throat, bronchitis, vaginal troubles, urinary discharge, ulcers, typhoid, eye sore, vomiting, syphilis, snake bite, scropion sting, piles, diphtheria and malignant throat diseases (Subramoniam, 2016a).

Antiarthritic activities: Mangiferin has documented antioxidant and anti-inflammatory effects. *In vivo* and *in vitro* anti-inflammatory activity of *M. indica* extract has been reported (Garrido *et al.*, 2004). A standard aqueous extract of *M. indica*, used in Cuba as an antioxidant under the brand name of VIMANG, was tested *in vivo* for its anti-inflammatory activity. *M. indica* extract, administered topically (0.5-2 mg per ear), reduced ear edema induced by arachidonic acid and phorbol myristate acetate in mice. *M. indica* extract also reduced myeloperoxidase activity. This extract (p.o.) reduced the serum levels of tumor necrosis factor alpha (TNF-α) in both models of inflammation. *In vitro* studies were performed using the macrophage cell line RAW264.7 stimulated with pro-inflammatory stimuli (LPS-IFNγ or the calcium ionophore A23187) to determine PGE_2 or LTB4 release, respectively. The extract inhibited the induction of PGE_2 and LTB4. *M. indica* extract also inhibited human synovial secretory phospholipase A_2 activity (Garrido *et al.*, 2004). The anti-inflammatory action of the extract would be related with the inhibition of iNOS and cyclooxygenase-2 expression (Beltran *et al*., 2004). The extract also showed analgesic activity in acetic acid-induced abdominal constriction and formalin-induced licking in mice (Garrido *et al*., 2001).

Other activities: Mangiferin isolated from the plant leaves possesses significant antidiabetic properties in streptozotocin-induced diabetic rats (Muruganandan *et al*., 2005). Mangiferin prevented diabetic nephropathy progression in streptozotocin-diabetic rats (Li *et al.*, 2010b). Recent studies shed light on the likely emergence of this compound as a very important molecule in mediating insulin sensitivity and modulating lipid metabolism (Mirza *et al*., 2013). Extracts of kernel of *M. indica* seeds also exhibited antidiabetic effect (Petchi *et al.*, 2011). 1,2,3,4,6 penta-O-galloyl-β-D-glucose isolated from *M. indica* inhibited 11-β-HSD-1 and ameliorated high fat diet induced diabetes in C57bL/6 mice (Mohan *et al.*, 2013). Antidiabetic compounds 6-O-galloyl-5-hydroxy mangiferin, mangiferin, 5-hydroxy mangiferin and methyl gallate werte isolated from the kernel of *M. indica*. These compounds reduced the blood glucose levels in alloxan induced diabetic rats (review: Firdous, 2014).

Mango fruit peel supplementation resulted in remarkable anti-diabetic effects in streptozotocin-induced diabetic rats (Gondi *et al*., 2014). Phenolic compounds identified in the raw and ripe mango peel include gallic acid, syringic acid, mangiferin, ellagic acid, gentisyl-protocatechuic acid and quercetin (Ajila *et al*., 2010). It is of interest to note that these compounds are known antidiabetic agents (Wei *et al*., 2012; Liu *et al*., 2008; Varma *et al*., 1975; Ueda *et al*., 2004). Mangifein exerts its antidiabetic activity through multiple mechanisms including modulation of insulin sensitivity and lipid metabolism (Latha and Daisy, 2011; Subramoniam, 2016a).

M. indica has been reported to possess antiviral, antibacterial, cardioprotective and immune modulatory activities (Makare *et al*., 2001; Garrido *et al*. 2005). Mangiferin from the leaves of *M. indica* has antihyperlipidemic and antiatherogenic properties in rats (Muruganandan *et al.*, 2005). Mangiferin exhibited antibacterial activity *in vivo* against specific periodontal pathogens such as *P. intermedia* and *P. gingivalis* (Bairy *et al.*, 2002). Anthelminthic and antiallergic activities of mangiferin have been reported (Garcia *et al*., 2003). *M. indica* extract protected the injury associated with hepatic ischaemia reperfusion (Sanchez *et al*., 2003). Flavonoids from *M. indica* are effectiveness for dyslipidemia (Anila and Vijayalakshmi, 2002).

Phytochemicals: Phytochemicals reported in *M. indica* include 2-octene, alanine, alpha-phellandrene, alpha-pinene, ambolic acid, ambonic acid, arginine, ascorbic acid, beta-carotene beta-pinene, carotenoids, furfurol, gaba, gallic acid, gallotannic acid, geraniol, histidine, isoleucine, isomangiferolic acid, kaempferol, limonene, linoleic-acid, mangiferic-acid, mangiferine, mangiferol, mangiferolic acid, myristic acid, neo-beta-carotene-b, neoxanthophyll, nerol, neryl-acetate, oleic acid, oxalic acid, p-coumaric acid, palmitic acid, palmitoleic acid, pantothenic acid, phenylalanine, phytin, quercetin, xanthophylls (Subramoniam, 2016a).

7. *Piper longum* L., Piperaceae, syn: *Piper aromaticum* Lam.

P. longum is commonly known as long pepper, thippali, *etc*. It is a native of the Indo-Malaya region. Fruit of *P. longum* is a valuable spice.

Plant description: *P. longum* is a slender, climbing, under shrub, creeping and rooting below. The young shoots are downy; the leaves are 5-10 cm long, 5 cm wide, ovate, cordate with broad rounded lobes at the base, sub-acute and entire.

Traditional medicinal uses: It is also used as a therapeutic agent in the treatment of various pathological conditions in ethnomedicine. It is used in cold cough, asthma, hoarseness and snake bite. In rheumatism, roasted aments are bitten up with honey and taken. In Java and Indonesia, the plant has been used topically for inflammation and muscular pain (Chauhan *et al*., 2011).

Antiathritic activities: *P. longum* fruit showed anti-inflammatory activity against carragenin induced hind paw edema in rats (Sharma and Singh, 1980). Further, aqueous extract of the fruits of the plant *P. longum* (200 and 400 mg/kg p.o.) showed potentially useful anti-arthritic activity against Freunds adjuvant induced arthritis in rats. The administration of extract resulted in significant reduction in paw swelling on 4^{th}, 8^{th}, 14^{th} and 21^{st} day after sub-plenter administration of Complete Freunds adjuvant. Furthermore, these results were supported by radiographic analysis of affected knees of rats (Yende *et al*., 2010).

Other activities: Ethyl acetae and ethanol extracts of *P. longum* fruits showed antihyperglycemic activity and attenuated oxidative stress in streptozotocin diabetic rats. The water extract of *P. longum* root (200 mg/kg) was found to possess significant antidiabetic activity after 6 h of the treatment in streptozotocin diabetic rats. The administration of the same dose of the extract for 30 days to streptozotocin-induced diabetic rats resulted in a significant decrease in fasting blood glucose levels with the corrections of diabetic dyslipidemia compared to untreated diabetic rats (Subramoniam, 2016a). Other reported pharmacological properties include anti-amoebic, antiasthmatic, hepatoprotective and immune modulatory activities (Chauhan *et al*., 2011).

Phytochemicals: Major chemical constituents are piperine, piperlongumine, piperlonguminine and methyl 3,4,5-trimethoxycinnamate. Others include resis, volatile oil, starch, fatty oil and so on (Chauhan *et al*., 2011).

8. *Piper nigram* L., Piperaceae

It is commonly known as black pepper in English, kali mirch in Hindi, pippali in Sanskrit and milagu in Tamil. Black pepper is native to south India and is extensively cultivated there and elsewhere in tropical regions like Brazil, Indonesia and Vietnam. Currently, Vietnam is the world's largest producer and exporter of pepper.

Plant description: The pepper plant is a perennial vine growing up to 4 m in height on supporting trees, poles, or trellises. It is a spreading vine, rooting readily where trailing stems touch the ground. The leaves are alternate, entire, 5 to 10 cm long and 3 to 6 cm across. The flowers are small, produced on pendulous spikes 4 to 8 cm long at the leaf nodes, the spikes lengthening up to 7 to 15 cm as the fruit matures. The fruit of the black pepper is called a drupe and when dried is known as a peppercorn.

Traditional medicinal uses: Traditionally, black pepper has been used in a variety of different remedies and for different purposes. According to Ayurveda, the pungency and heating properties of black pepper work to help metabolize food as it is digested in our system. Peppercorns are also being employed in traditional medicines in treating flatulence and indigestion.

Antiarthritic activities: Anti-inflammatory and antiarthritic effects of piperine have been shown in human interleukin 1-β-stimulated fibroblast-like synoviocytes and in *in vivo* rat arthritis models (Bang *et al*., 2009). Piperine treated (10-100 µg/ml) synoviocytes were found to reduce the synthesis of prostaglandin E_2. The expression of interleukin-6 and matrix mettalo-proteinase-13 were also inhibited. The migration of activator protein-1 into the nucleus in interleukin 1-β treated synoviocytes was inhibited by piperine. The pain and arthritic symptoms in rats were significantly reduced by piperine (Bang *et al*., 2009). Intra-peritoneal injection of piperine (30 and 50 mg/kg) resulted in significant analgesic activity in acetic acid- induced writhing and tail flick assay models in mice. The analgesic activity of piperine was reversed in the tail-flick assay on pretreatment of rats with naloxone which suggests that the analgesic activity of piperine is mediated *via* opioid pathway (Bukhari *et al*., 2013).

Black pepper showed promising antioxidant activity also. Under *in vitro* conditions, it inhibited the production of free radicals and reactive oxygen species. *P. nigram* or piperine was also found to decrease lipid peroxidation *in vivo*. Further, methanolic extract of *P. nigram* ameliorated β-amyloid-induced spatial memory deterioration by depletion of the oxidative stress in the hippocampus of rats. The extract also ameliorated atherogenic diet induced oxidative stress in rats (review: Damanhouri and Ahmad, 2014).

Other activities: Other reported pharmacological activities of black pepper include antihypertensive activity, antiasthmatic activity, antimicrobial activity, anticancer activity, hepatoprotective activity, antidiarrheal activity, digestive activity, antidepressant activity, immunomodulatory activity profertility activity and anti-convulsant activity. It is also reported to stimulate cognitive function. Piperine increases bioavailability of many drugs and nutrients by inhibiting various metabolizing enzymes (Damanhouri and Ahmad, 2014).

Phytochemicals: Compounds isolated from black pepper include brachyamide B, dihydro-pipericide, (2E,4E)-N-eicosadienoyl-pereridine, N-trans-feruloyltryamine, N-formylpiperidine, guineensine, pentadienoyl piperidine, (2E,4E)- nisobutyl decadienamide, isobutyl-eicosadienamide, tricholein, trichostachine, isobutyl-eicosatrienamide, isobutyl-octadienamide, piperamide, piperamine, piperettine, pipericide, piperine (an amine alkaloid), piperolein B, sarmentine, sarmentosine and retrofractamide (Damanhouri and Ahmad, 2014).

9. *Punica granatum* L., Lythraceae (formerly Punicaceae)

Common names of *P.granatum* include pomegranate, wild pomegranate, bijapura, anar, anara, madulai and matalam. It is considered to be the native of Iran, Afghanistan and Baluchistan, cultivated throughout India and found wild in the warmer valleys and outer hills of the Himalaya between altitudes of 900-1800 m. Now, it is cultivated in many countries.

Plant description: A shrub or small tree with smooth, dark grey bark attaining a height of about 10 m. Branchlets sometime spiniscent; leaves oblong or obovate, shining above. Scarlet red or yellow flowers produced solitary or 1-4 flowers together. Fruit is a globose balusta, crowned with persistant calyx, rind woody and coriaceous, interior septa containing variously coloured seeds with fleshy testa. Seeds are numerous, red, pink or yellowish white (Subramoniam, 2016a).

Traditional medicinal uses: In Iranian traditional medicine the seeds and fruit juice are considered as tonic for the treatment of rheumatism. All parts of this plant such as leaves, fruit, fruit peel and seeds are used in traditional medicine. It is astringent, refrigerant, cardiotonic, stomachic, stimulant, taenifuge, vermifuge, anthelmintic, purgative and used in diarrhea, dysentery, leucorrhoea, scorpion venom, worms, dyspepsia, hydrocele, inflammation, sore-throat, sore-eye, brain disease, spleen complaints, chest troubles, scabies, bronchitis, ear aches, biliousness, liver and kidney disorders, asthma, dermatosis, metrorrhagia, piles, tape worm attack and tumour (WHO, 2009).

Antiarthritic activities: Consumption of pomegranate extract potently delayed the onset and reduced the incidence of collagen-induced arthritis in mice. Severity of arthritis was also significantly lower in the extract-fed animals. Histopathology of the arthritic joints from pomegranate extract-fed mice demonstrated reduced joint infiltration by the inflammatory cells, and the destruction of bone and cartilage was alleviated. Levels of IL-6 were significantly decreased in the joints of the extract-fed mice with arthritis. In mouse macrophages, pomegranate extract abrogated multiple signal transduction pathways and downstream mediators implicated in the pathogenesis of rheumatoid arthritis (Shukla *et al*., 2008). In an *in vitro* study, *P. granatum* extract inhibited Il-1beta induced expression of matrix metalloproteinases by inhibiting the activation of MAP kinases and NF-kappaB in human chondrocytes (Ahmed *et al.*, 2005). Pomegranate fruit consumption reduced composite disease activity index in rheumatoid arthritis patients. In a pilot study on rheumatoid arthritis patients, consumption of pomegranate decreased serum oxidative stress and reduced disease activity in patients with active rheumatoid arthritis (Balbir-Gurman *et al.*, 2011).

Various parts of the plants including fruit juice and peel have properties such as antioxidant, hypolipidemic and anti-inflammatory properties. Polyphenols from pomegranate fruit showed strong antioxidant properties (Mertens-Talcott *et al*., 2006). Anti-inflammatory properties of a pomegranate extract and its metabolite urolithin-A has been reported in a colitis rat model (Larrosa *et al*., 2010). Interestingly, it has been reported that pomegranate juice sugar fraction reduces macrophage oxidative state, whereas white grape juice sugar fraction increases it (Rozenberg *et al*., 2006).

Other activities: Pomegranate juice reduces oxidized low-density lipoprotein down regulation of endothelial nitric oxide synthase in human coronary endothelial cells (de Nigris *et al.*, 2006). In preliminary laboratory research and human pilot studies, juice of the pomegranate was effective in reducing heart disease risk factors, including low-density lipoprotein oxidation, macrophage oxidative status, and foam cell formation (Esmaillzadeh *et al.*, 2004; Kaplan *et al*., 2001). The pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduced common carotid intima-media thickness, blood pressure and inhibits low-density lipoprotein (LDL) oxidation (Aviram *et al*., 2004). In atherosclerotic mice and in humans, pomegranate juice flavonoids inhibit LDL oxidation and cardiovascular diseases (Aviram *et al*., 2004; Huang *et al*., 2005).

Several studies suggest that the fruit peel extract can also ameliorate the complications of DM. Methanol extract of the fruit peel (200 mg/kg) increased the activities of antioxidant enzymes and decreased oxidative stress in the kidney and liver of alloxan-induced diabetic rats (Parmar and Kar, 2007). Further, the methanol extract reduced the levels of lipid peroxides in heart, kidney and liver; it improved the levels of serum insulin and thyroid hormones in the diabetic rats (Parmar and Ka, 2008). Besides, the peel-extract improved lipid profiles and oxidative stress favorably in the experimental diabetic rats (Althunibat *et al*., 2010). An antidiabetic principle has been isolated from methanol extract of fruit rinds of *P. granatum*; the compound, valonic acid dilactone (25 or 50 mg/kg, p.o.) showed promising dose dependent antidiabetic activity (Jain *et al*., 2012). The methanol extract (400 mg/kg) or valonic acid dilactone treatment resulted in very minimal acinar damage and adequate number of pancreatic islets in the diabetic rats. Valonic acid dilactone was found to act through several mechanisms which include inhibition of aldose reductase, α-amylase and PTP1B (Jain *et al*., 2012). The presence of antidiabetic compounds such as ursolic acid, gallic acid, ellagic acid, kaempferol, and epigallocatechin 3-gallate in the fruit has been reported. Concentrated pomegranate juice improved lipid profiles in diabetic patients with hyperlipidemia (Esmaillzadeh *et al*., 2004).

Other reported activities include antiviral, antimicrobial, immunomodulatory and cardiovascular protective effects (review: Middha *et al*., 2013). Pomegranate juice consumption inhibits serum angiotensin converting enzyme and reduces systolic blood pressure (Aviram and Dornfeld, 2001). Pomegranate juice, total pomegranate ellagitannins, and punicalagin suppressed inflammatory cell signaling in colon cancer cells (Adams *et al*., 2006). Several studies strongly suggest that the fruit extracts and seed have anticancer activity (Subramoniam, 2016a). Anticancer activities of pomegranate extracts and genistein were shown in human breast cancer cells (Jeune *et al*., 2005). Pomegranate extract is active against bacteria including drug resistant bacteria (Voravuthikunchai and Kitpipit, 2005). The fruit juice has anti-HIV-1 activity (Neurath *et al*., 2004). Seed extracts have antidiarrhoeal activity in rats (Das *et al*., 1999). Pomegranate flower extract possesses potent antioxidant activity and abrogates Fe-NTA induced hepatotoxicity in mice (Kaur *et al.*, 2006). Pomegranate extract improved a depressive state and bone properties in menopausal syndrome model ovariectomized mice (Mori-Okamoto *et al*., 2004).

Pomegranate ellagitannin punicalagin is not toxic to rats contrary to earlier report about its toxicity to cattle. Repeated oral

administration of a 6 % punicalagin-containing diet for 37 days did not result in any significant adverse effects except a decrease in blood urea and triglyceride and initial reduction in growth rate. In animal experiments, intragastic administration of very large doses of the alkaloids from the bark caused respiratory arrest and death (WHO, 2009; Subramoniam, 2016a).

Phytochemicals: Compounds from seed include coniferyl 9-O-[beta-D-apiofuranosyl(1–>6)]-O-beta-D-glucopyranoside, sinapyl 9-O-[beta-d-apiofuranosyl(1-6)]-O-beta-D-glucopyrano-side, 3,3'-di-O-methylellagic acid , 3,3',4'-tri-O-methylellagic acid , phenethyl rutinoside, icariside D1, and daucosterol. The fruit contains anthocyanidins: delphinidin, cyanidin, pelargonidin, punic acid, estrone, isomer of elaeostearic acid, 3,5 diglucoside, delphinidin diglucoside, isoqurcetrin, petunidin derivatives, pelletierine, pseudo-pelletierine, methyl-pelletierine, methyl-isopelletierine, friedelin, betulic acid, ursolic acid, 2-92-propenyl)-delta-piperideine, Cyaniding-3-glucoside, cynidin-3,5-diglucoside, granatin A and B, corilagin, strictinin, punicalin, punicalagin, nonadecanoic acid, heneicosanoic acid, tricosanoic acid, 13-methyl stearic acid, 4-methyl auric acid. The plant contains betainic alkaloid, punicalagin, ellagic acid, tannins, flavonoids, *etc*. The fruit peel contains bioactive compounds such as casuarine, corilagin, ellagic acid, gallic acid, methyl gallate, granatin A and B, peduncularin, punicalagin and punicalin. Flavonoids of pomegranate peel include catechin, cyaniding, epicatechin, epigallocatechin 3-gallate, flavan-3-ol, kaempferol, kaempferol-3-O-glucoside, kaempferol-3-O-rhamnoglycoside, luteolin, luteolin-3-0-glucoside, naringin, pelargonidin, quercetin and rutin (Subramoniam, 2016a).

10. *Syzygium cumini* (L.) Skeels., Myrtaceae, syn: *Eugenia jambolana* (Lam.) DC.

S. cumini is commonly known as black berry, black plum (Eng.), Jambah, jamun, arugadam, njaval (Indian languages). *S. cumini* occurs in India, Subtropical Himalaya, Sri Lanka, Malaysia, Australia and elsewhere.

Plant description: *S. cumini* is a tree of 25-35 m height, branchlets glabrous; leaves decussate, elliptic or ovate-lanceolate, coriaceous, glossy above with entire margin; flowers are in axillary or terminal cymose panicle. Fruit is a globose berry with solitary seed.

Traditional medicinal uses: Bark, fruit, flower and seeds are used in traditional medicine. It is used in Ayurveda and Yunani medicines against diabetes, dysentery, asthma, sore throat and bronchitis. It is considered as acrid, sweet, digestive, astringent, antihelmintic, tonic, diuretic, refrigerant and carminative; it is used in thirst, biliousness, blood diseases, ulcers, stopping urinary discharge, diarrhea, anemia, cancer and colic (Subramoniam, 2016a).

Anti-inflammatory and antioxidant activities: The extracts of *S. cumini* seed possess varying degree of anti-inflammatory activity when tested at various doses. The methanol extract (400 mg/kg) showed highly significant anti-inflammatory activity at 4 h, where it caused 62.6% inhibition (review: Sharma *et al.*, 2012). *S. cumini* exhibited anti-inflammation property against indomethacin-induced acute gastric ulceration and inflammation (Chanudom and Tangpong, 2015). Besides, the seed inhibited autacoid-induced inflammation in rats (Murugananthan *et al.*, 2002). Tannins extracted from *S. cumini* fruit showed a very good DPPH radical scavenging activity and ferric reducing/antioxidant power. The effective dose for antioxidant activity is about 500 µg (review: Sharma *et al.*, 2012; Jacob and Titus, 2009).

Other activities: Several studies have establishedthe antidiabetic properties of *S. cumini*. The hypoglycemic and antihyperglycemic activities of 90 % ethanol extract of whole fruit of *S. cumini* in normal and streptozotocin-induced diabetic rats have been reported (Gupta and Saxena, 2011). The fruit extract exhibited blood glucose lowering activity in fasted, fed and streptozotocin diabetic rats at a single oral dose of 250 mg/kg. Further, it increased glycogen content in muscle along with marked degranulation in pancreatic β-cells (Gupta and Saxena, 2011). Antihyperglycemic effect of the water extract of *E. jambolana* has been shown in fruit pulp in normal and alloxan-induced diabetic rabbits (Sharma *et al.*, 2006). An anti-hyperglycemic compound, α-hydroxy succinamic acid, was isolated from the fruits of *S. cumini*; this compound attenuated renal dysfunction in streptozotocin diabetic rats (Tanwar *et al.*, 2010). It should be noted that antidiabetes mellitus compounds, ellagic acid, gallic acid, quercetin, β-sitosterol, ferulic acid, kaempferol glycosides etc were isolated from this plant.

Tannins extracted from the plants have gastroprotective activities (Ramirez and Rao, 2003). Antibacterial activity of *S. cumini* leaf essential oils has been reported (Shafi *et al.*, 2002). Other reported activities include, antiallergic, antinociceptive, chemopreventive and antifungal activities (review: Sharma *et al.*, 2012).

Phytochemicals: The plant is rich in anthocyanin containing compounds, glucoside, ellagic acid, isoquercetin, kaemferol, gallic acid and myrectin. Other reported compounds include, myricetin-3-L-arabinoside, dihydromyricetin, quercetin-3-D-galactoside, beutulinic acid, friedelin, friedelinol, kaempferol-3-O-glucoside, quercetin, β-sitosterol, stigmasterol, lupeol, hepatocosane, triacontane, hentriacontane, octacosanol, triacosanol, dotriacosanol, crotegolic acid, delphinidine-3-gentiobioside, malvidin-3-laminaribioside, petunidin-3-gentiobioside, corilagin, ellagitannins, 3-6 hexahydroxydiphenoyl glucose, caffeic acid, ferulic acid, guaiacol, resorcinol dimethyl ether, veratrole, vernolic acid, malvalic acid (Gupta and Saxena, 2011; Subramonim, 2016a).

11. *Trigonella foenum-graecum* L., Leguminoceae

Trigonella foenum-graecum is commonly known as fenugreek (Eng.), methi, uluva, methika, *etc*. (Indian languages). *T. foenum-graecum* is Native to North Africa and countries bordering the eastern Mediterranean; fenugreek grows in open areas and is widely cultivated for its edible seed (used in food preparations as spice, *etc*.) notably in India. The seeds are collected during the autumn.

Plant discription: Fenugreek is an erect annual, aromatic herb, growing about 2 feet high; flowers 1-2, axillary, sessile, corolla much exerted. Pod 5-7.5 cm long with a long persistent beak. The seeds are brownish, oblong, rhomboidal, with a deep furrow dividing them into two unequal lobes. They contained ten to twenty together, in long, narrow, sickle-like pods (Subramoniam, 2016a).

Traditional medicinal uses: Fenugreek seeds and leaves are used as food and medicine. Fenugreek has a long history of dubious indications, including fevers, colic, flatulence, dyspepsia, dysentery, cough, tuberculosis, edema, rickets, leg ulcers, gout, diabetes and baldness. Fenugreek is known in Ayurveda as methika, and has been used in a number of ayurvedic preparations for its carminative, galactagogue and antidiabetic properties. The leaves are applied

externally in the form of poultice for swelling, burns, boils, abscess and ulcers. Seeds are good for fever, vomiting, anorexia, cough, bronchitis and colonitis. An aqueous extract of seeds possesses antibacterial property (Subramoniam, 2016a).

Antiarthritic activities: An aqueous fraction of fenugreek has been reported to have the highest antioxidant activity. The seed extract at high concentrations has been shown to act as a scavenger of free radicals indicating that the extract of fenugreek seeds protects cellular structures from oxidative damages. Fenugreek leaf extract possessed anti-inflammatory activity against formalin-induced edema in rodents (Ahmadiani *et al.* 2001; Patil and Jain, 2014).

Fenugreek mucilage exhibited antiarthritis activity also. It showed maximum percentage of edema inhibition in adjuvant induced arthritis in rats at a dose of 75 mg/kg on 21st day of adjuvant arthritis. The effect was higher than that of standard drug indomethacin. The activities of cyclooxygenase-2 (COX-2) and myeloperoxidase and concentration of thiobarbituric acid reactive substance were decreased and the activities of antioxidant enzymes, vitamins C and reduced glutathione level were increased on treatment with fenugreek mucilage. The increment in ESR and total WBC, reduction in RBC count and hemoglobin and aberrant changes to the C-reactive protein levels observed in the arthritic animals were also found to be significantly restored in fenugreek mucilage treated rats. Histopathology of paw tissue showed decreased edema formation and cellular infiltration on supplementation with fenugreek mucilage. Thus, the results demonstrated the potential beneficiary effect of fenugreek mucilage on adjuvant induced arthritis in rats (Sindhu *et al.*, 2012).

Other activities: The ethanol extract of *T. foenum-graecum* seeds exhibited hypoglycemic effects in alloxan-induced diabetic rats (Mowla *et al.*, 2009). In another study, water and ethanol extract of fenugreek exhibited antidiabetic activity in alloxan induced diabetic rats (Rajarajeswari *et al.*, 2012). Fenugreek seeds contain 4-hydroxy isoleucine in 2 diastero isomers: the major one being the (2S, 3R, and 4S) configuration and the minor one being the (2R, 3R and 4S) configuration. The ability of the major isomer to stimulate glucose-induced insulin secretion in micro molar concentrations was shown (Sauvaire *et al.*, 1998). Trigonelline is a major alkaloid present in fenugreek. The isolated pure trigonelline (10 mg/kg., twice a day, for 4 weeks), exhibited a significant hypoglycemic effect in normal and alloxan diabetic rabbits, but its effect was more in diabetic animals compared to normal animals(Al-Khateeb *et al.*, 2012). In another study, administration of trigonelline to alloxan diabetic rats helped to protect β-cells from death and damage. Further, trigonelline treatment decreased intestinal α-amylase, maltase and lipase; the treatment resulted in decrease in blood glucose, cholesterol and triglycerides in the diabetic rats (Hamden *et al.*, 2013). An anti-hyperglycemic compound named GII was purified from the water extract of the seeds of *T. foenum-graecum* and shown to be different from trigonelline. GII (50 mg/kg, p.o.) reduced blood glucose in glucose tolerance test in the sub-diabetic and moderately diabetic rabbits (Moorthy *et al.*, 2010a; Moorthy *et al.*, 2010b). In another study, administeration of GII (50 mg/kg for 15 days) to subdiabetic and moderately diabetic rabbits or (50 mg/kg for 30 days) to severe diabetic rabbits, corrected or almost normalized the altered serum lipids, liver glycogen, enzymes of glycolysis, glyconeogenesis, glycogen metabolism, polyol pathway and antioxidant enzymes. GII (50 mg/kg) treatment improved serum HbA1C and insulin levels also in these rabbits (Puri *et al.*, 2012; Patil and Jain, 2014; Subramoniam, 2016a). Several human clinical studies have shown the usefulness of fenugreek seeds in management of both type-1 and type-2 diabetes mellitus. Fenugreek has been shown to reduce fasting and postprandial blood glucose levels in diabetic patients (Subramoniam, 2016a). Other reported activities include anti-neoplastic effect. Alcohol extract of the seed inhibited growth of Ehrlich ascites carcinoma cells in mice. Fenugreek seed extract also significantly inhibited the 7,12-dimethylbenz (α) anthracene induced mammary hyperplasia in rats (Patil and Jain, 2014).

Antihypercholesterolemic effect of fenugreek seed has been shown in animals. In a few clinical studies also penugreek seed showed hypolipidemic effects (Ambili and Subramoniam, 2005). There is little evidence to suggest that fenugreek is toxic or that it has significant anticoagulant or hormonal effects. No acute toxicity was observed for the ethanol extract of the seeds when administered oraly at a high dose of 3 g/kg (Mowla *et al.*, 2009).

Phytochemicals: The ethanol extract of the seeds showed the presence of alkaloids, steroids and carbohydrates (Mowla *et al.*, 2009). The seeds of *T. foenum-graecum* contain sapogenins such as diosgenin, hederagin, tigogenin, neotigogenin, yuccagenin, gitogenin, smilagenin, sarsasapogenin and yamogenin together with glycosides like foenugracein, trigoneosides 1a, 1b, 11a, 111a, IVa, Vb, VI, VIIb, VIIIb, trigofoenosides A, B, C, D and fenugrin B. Several coumarin compounds have been identified in seeds, *viz.*, 3, 4, 7 trimethyl coumarin, 4-methyl coumarin and trigocoumarin. The seeds also contain several alkaloids such as trigonellin, gentianine, carpaine and C-type glycoside flavones such as vitexin, isoorientin, isovitexin, saponaretin and tricin. Minor steroidal sapogenin such as smilagenin, sarsasapogenin and yuccagenin were also identified in seeds (Patil and Jain, 2014).

12. *Zingiber officinale* Rosc., Zingiberaceae

Z. officinale is commonly known as ginger (Eng.), inchi, ardraka, adark, allam, inji (in India), *etc.* It is widely cultivated in India and other parts of tropical Asia for its valued rhizome (used as spice, food additive, etc).

Plant description: *Z. officinale* is a rhizomatous biennial plant with lanceolate leaves, glabrous beneath, clasping the stem by their long sheath. Spikes produced from the root-stock are more or less elongated peduncles with sheathing scariose bract leaves. Fruit is a dehiscent capsule.

Traditional medicinal uses: It is antiseptic, anodyne, apertif, aphrodisiac, astringent, carminative, digestive, expectorant, pedeculicide, rubefacient, sialagogou, sternutatory, stimulant, stomachic, sudorific and used in asthma, amenorrhoea, back ache, bronchitis, cancer, colic, cataplasm, cholera, dog bite, congestion, cough, diarrhoea, dysentery, fever, fistula, dyspepsia, fatigue, flatulence, gingivitis, flu, head ache, hepatosis, gout, indigestion, laryngitis, malaria, nausea, paralysis, phthisis, rabies, puerperium, rheumatism, snake bite, rhinosis, sores, menstruation ailments, stomach ache, swelling, tooth ache and tetanus (Subramoniam, 2016a).

Antiarthritic activity: Ginger extracts have beneficial effects in osteoarthritis and inflammation (Blíddal *et al.*, 2000). Rhizome of

ginger is a potential anti-inflammatory and antithrombotic agent. The ginger extract has antioxidant, hypocholesterolemic, and anti-atherosclerotic activities in mouse models (WHO, 1999). Several experimental studies have shown that extracts of ginger can ameliorate the toxicity through enhancing the antioxidant status (Ajith, 2010). Further its protective effect against Fe^{2+}, H_2O_2 – EDTA (Fenton reaction) induced lipid peroxidation in various tissues especially brain and mitochondria or protection against DNA damages has been demonstrated. The results show that ginger extract contains a strong antioxidant system that prevents lipid peroxidation in tissues (Subramoniam, 2016a). It is a potent anti-inflammatory agent and the active principles include sesquiterpene lactones (Kaur *et al.*, 2012). Ginger extract inhibited the production of prostaglandins and leukotrienes (Kiuchi *et al.*, 1992). Ginger extract components suppressed induction of chemokine expression in human synoviocytes. Single or formulations with *Z. officinale* has been used in the treatment of RA in traditional medicine. In a human clinical study, ginger has been reported to be beneficial to arthritic patients. More than 70 % of the patients (out of 28 RA, 18 OA and 10 muscular discomfort patients) experience varying degrees of relief from pain and swelling. None of the patient reported adverse effects during the treatment period from 3 months to 2.5 years. Ginger is an inhibitor of both prostaglandin and leukcotrine biosynthesis and the authors suggest that its beneficial effects could be, to a large extent, due to these inhibitory effects (Srivastava and Mustafa, 1992; Srivastava and Srimal, 1985).

Other activities: In a clinical study on coronary artery patients, a single dose of 10 g dry powdered ginger (p.o.) produced significant reduction in platelet aggregation induced by ADP or epinephirine. Another study has shown that 5 g powderd ginger given daily to healthy subjects for 7 days reduced the fat- related increase in ADP-and epinephrine induced platelet aggregation which was brought to normal level (Verma *et al.*, 1993; Bordia *et al.*, 1997). The antioxidant activity of ginger has been demonstrated in normal people as well as in patients with CAD. Ginger administration (5g/ day for 4 weeks) significantly decreased lipoprotein oxidation (Verma *et al.*, 2004). Ginger extract significantly reduced the development of plaque formation and LDL-cholesterol level with a concomitant increase in serum HDL cholesterol. Thus, moderate use of ginger could prevent lipid peroxidation that leads to heart diseases and DNA damages. Ginger has antiplatelet activity also (Subramoniam and Satyanarayana, 1989).

In alloxan diabetic rats, ginger lowered blood glucose levels. It also showed antidiabetic activity in streptozotocin indued type 1 diabetic rats. Further, ginger enhanced insulin sensitivity in adipocytes. The ethanol extract of ginger exhibited significant lipid lowering and antilipid peroxidation activities in diabetic rats (Subramoniam, 2016a). The rhizome extract of this plant exhibited antidiabetes and antioxidant effects in alloxan-induced and insulin resistant diabetic male rats. The treatment reduced fasting blood glucose levels and increased insulin level and also enhanced insulin sensitivity in these diabetic rats (Iranloye *et al.*, 2011). Alcohol extract of the rhizome attenuated progression of diabetic structural nephropathy in streptozotocin-diabetic rats (Ramudu *et al.*, 2011). 6- Shogaol and 6-gingerol, the pungent of ginger, inhibited TNF-α mediated downregulation of adiponectin expression *via* different mechanisms in 3T3-L1 adipocytes (Wang *et al.*, 2014). These studies suggest the potential of ginger for the preparation of a food supplement to diabetic patients.

The rhizome juice increased sperm count and motility. In a clenical study, ginger has been reported to be useful for nausea and vomiting in pregnancy. Ginger has antiviral properties and antirhinoviral sesquiterpenes have been isolated. The essential oils of ginger have antimicrobial activity. Ginger juice inhibited rat ileal motility *in vitro* (WHO, 1991). Ginger also showed protective effects against damages caused by anticancer drugs (Ajith *et al.*, 2008). Ginger oil has been shown to prevent skin cancer in mice and a study at the University of Michigan demonstrated that gingerols can kill ovarian cancer cells. Effects of ginger on gastro intesinal movements have been described by some workers (Yamahara *et al.*, 1990). The extract of ginger appears to be safe in rats (WHO, 1991). Further, ginger is used as an ingrident of diet from ancient time onwards without any recored toxicity at reasonable doses.

Phytochemicals: Phytochemicals reported include sesquiterpenene alcohol, chavicol (phenol), esters of acetic and caprylic acid, α and β zingiberene, ar-curcumine, franesene, β-bisabolene, r-selinene, β-elemene, β-sesquiphellandrene, β-eudesmol, zingiberol, camphene, α and β-pinene, cumene, myrcene, limonene, p-cymene, β-phellandrene, boronyl acetate, linalool, n-nonanal, d-decanyl,methyl hepatenone,1-8-cineole, borneol, gingerol, shogaol, zingerone, oleoresin, gingerol, gingesulfonic acid (antiulcer principle), gingerglycolipids A, B and C, monoacyldigalactosylglycerols and geranyl disaccharide (WHO, 1999).

5. Antiarthritis activities of dietary compounds

Some of the common dietary phytochemicals with antiarthritis and/or strong anti-inflammatory properties along with antioxidant activities include Chlorophyll-a and its degradation products, curcumin (diferuloyl methane), epicatechin, mangiferin, quercetin and β-sitosterol.

1. Chlorophyll-a and its degradation products

In ethnomedical practices, in certain villages in Kerala State, India, the green leaves of many plants (*Streblus asper*, *Chromolaena odorata*, *Eupatorium odoratum*, *etc*.) are used to treat inflammation of joints and arthritis. The hot oil extract or a decoction of fresh leaves of these plants is applied on the inflamed joints. Search for active principles from the hot coconut-oil extract of *Streblus asper* led to the discovery of the anti-inflammatory properties of degradation products of chlorophyll-a (Subramoniam *et al.*, 2012). Chlorophyll-a is an essential molecule for photosynthesis in plants because of its role as primary electrol donar in the electron transport chain. Chlorophyll-a contains a central Mg ion encased in a 4-ion nitrogen ring. Methyl group and a long hydrocarbon tail (phytidyl chain) are attached to the porphyrin ring of chlorophyll-a. Pheophytin-a (Mg free chlorophyll-a) and pheophorbide (chlorophyll-a without Mg and phytidyl chain) are 2 major degradation products of chlorophyll-a. Since chlorophyll-a is present in the green leafy vegetables, *etc*., it is an ingredient of diet. Subramoniam and co-workers have shown for the first time that chlorophyll-a, a green pigment involved in photosynthesis, is also a promising pharmaceutical. Chlorophyll-a and its degradation products, (pheophytin-a and pheophorbide-a) exhibit promising anti-inflammatory activity against carrageenan-induced paw edema in mice and formalin-induced paw edema in rats (Subramoniam *et al.*, 2012). Further, these compounds showed antioxidant activities

also. Chlorophyll-a and its degradation products inhibited bacterial lipopolysccharide (LPS)-induced TNF-α gene expression in HEK293 cells. Chlorophyll-b only marginally inhibited both inflammation and TNF-α gene expression (Subramoniam *et al.*, 2012). The anti-inflammatory property of pheophytin-a and pheophorbide-a is confirmed by other workers in LPS-stimulated macrophage cells in culture (Islam *et al.*, 2013). TNF-α is a cytokine involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. It promoted many of the clinical problems associated with autoimmune disorders and hyper innate/adaptive immunity mediated diseases such as rheumatoid arthritis, alkylosing spondylitis and so on.

Other properties: Other reported activities of degradation products of chlorophyll-a include antioxidant activity and antimutagenic activity (Ferruzzi *et al.*, 2002). Further, these chlorophyll derivatives possess cancer preventive activity (Ferruzzi and Blakeslee, 2007).

2. Curcumin (diferuloyl methane)

It is the major active principle present in *Curcuma longa* rhizome. It showed antirheumatoid activity in human clinical trials. Chemical structure of curcumin is shown in Figure 1.

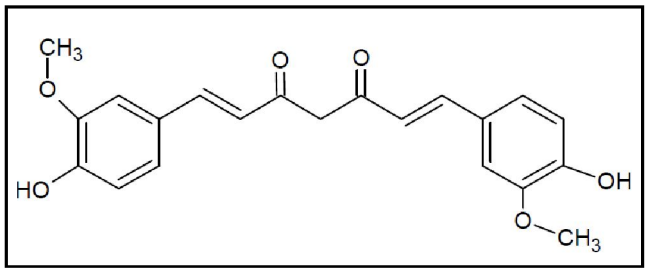

Figure 1: Structure of curcumin

Curcumin showed anti-inflammatory activity against carrageenan-induced paw edema in rats. Further, it showed antiarthritis activity against adjuvant-induced arthritis in rats (review: Subramoniam *et al.*, 2013).

Other activities: The compound improved insulin and leptin sensitivity in the liver of rats; it prevented hypertriglyceridemia and hepatic steatosis in fructose-fed rats. Curcumin, demethoxy-curcumin, sesquiterpenoids, bisdemethoxycurcumin, and ar-turmerone show antidiabetes mellitus activity *via* PPAR-γ ligand-binding activity. Further, curcumin can prevent some of the diabetic complications primarily due to its antioxidant and anti-inflammatory properties. Curcumin has potentiality to prevent carcinogenesis and suppress certain types of cancer growth. Curcumin is known to induce apoptotic cell death. However, it can prevent oxidative stress mediated apoptosis due to its antioxidant property. Other reported activities include antiviral activity, wound healing, hepato-protection from toxic chemicals and protective property on the cardio-vascular system (Subramoniam, 2016b).

3. Epicatechin

Epicatechin is a phenolic compound found in many plants includiung *Cinnamomum* sp, *Prunus amygdalus* and *Camelle sinensis*. Chemical structure of epicatechin is shown in Figure 2.

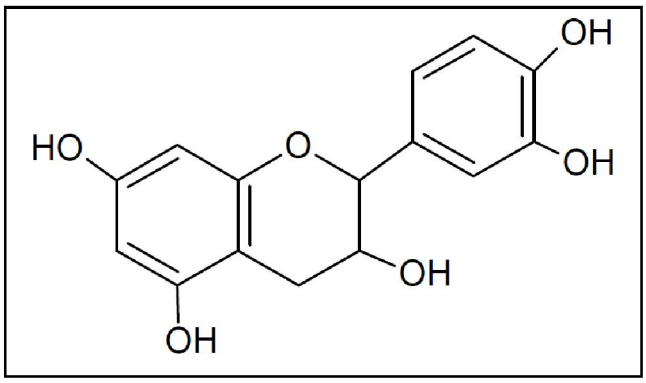

Figure 2: Structure of epicatechin

Epicatechin reduced inflammation in carrageenan induced edema, in cotton pellet granuloma model and in formaldehyde-induced arthritis in rats. It has promising antioxidant activities also (review: Subramoniam *et al.*, 2013). A related compound, epigallo-catechin gallate is a major compound in *C. sinensis* with strong antioxidant activity.

Other activities: Insulin release was enhanced by approximately 44-70 folds when isolated rat islets were exposed to epicatechin (0.8 mmol/l). Epigallo-catechin gallate isolated from *C. sinensis* leaf lowered hepatic glucose production. Further, epigallo-catechin gallate supplementation prevented progression to glucose intolerance in db/db mice. Catechins have been reported to have many pharmacological properties such as anti-oxidant activity, anti-inflammatory, anticarcinogenic, antiultraviolet radiation, and reduction of blood pressure, glucose and cholesterol levels. Besides, epicatachin increased the testosterone secretion by rat Leydig cells *via* the enzyme activities of 17β-hydroxysteroid dehydrogenase. Furthermore, epicatechin is useful in the treatment of gastric ulcers also. It provides gastroprotection through reinforcement of the mucus barrier and neutralization of gastric juice (Subramoniam, 2016b).

4. Mangiferin (xanthone)

Mangiferin is present in ripe mango peel, unripe mango, mango leaves and bark. It is also reported in other plants like *Anemarrhena asphodeloids* and *Salacia* sp. Chemical structure of mangiferin is shown in Figure 3.

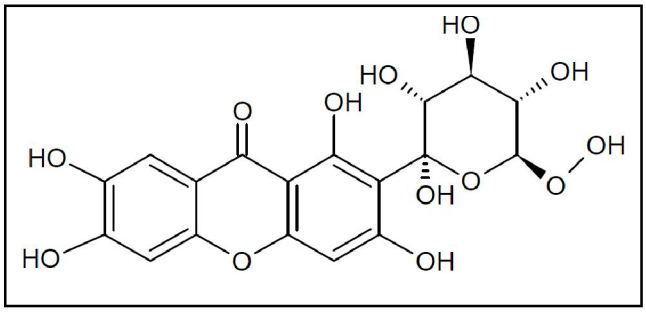

Figure 3: Structure of mangiferin

Mangiferin has potent antioxidant and anti-inflammatory properties. It exhibited anti-inflammatory activity in carrageenan induced edema in rats, in cotton pellet granuloma model of inflammation in rats

and in formaldehyde-induced arthritis in rats (review: Subramoniam *et al.*, 2013). Mangiferin stimulated mitochondrial function and ATP production and showed anti-oxidant properties. In primary macrophages from mice, mangiferin inhibited the expression of proinflammatory cytokines including IL-1 and TNF-α (Mirza *et al.*, 2013).

Other activities: Mangiferin enhances insulin sensitivity and modulates lipid metabolism. In rat myocytes, mangiferin fraction from *S. oblonga* increased GLUT4 mediated glucose uptake probably *via* activation of AMPK. Further, mangiferin activated the anti-hyperlipidemic transcription factor PPAR-α suggesting that the compound suppresses lipogenesis and stimulates lipolysis, thereby preventing high-fat-diet induced diabetes. In KK-Ay diabetic mice and streptozotocin-induced diabetic rats, mangiferin reduced plasma glucose and increased insulin sensitivity and glucose tolerance. Further, mangiferin is an inhibitor of α-glucosidase which could reduce glucose formation from carbohydrate in the intestine. This compound also induced the enzymes in glycolysis (hexokinase and pyruvate kinase) and the enzymes involved in glycogen synthesis (Mirza *et al.*, 2013). Mangiferin has potent cardioprotective, hypolipidemic, antihyperuricemic, anticancer, and antiviral activities. Mangiferin can modulate molecular targets such as NF-κB signaling, and COX-2 protein expression (Mirza *et al.*, 2013).

5. Quercetin

Quercetin (flavonoid) is present in many edible fruits and vegetables. These include *Citrullus lanatus*, *Cinnamomum* sp and *Phyllanthus emblica*. Chemical structure of quercetin is shown in Figure 4.

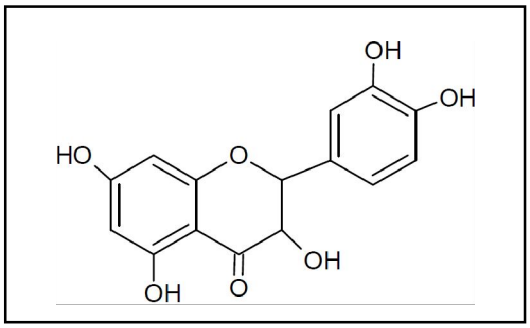

Figure 4 : Structure of quercetin

Quercetin showed promising anti-inflammatory and antioxidant properties (Subramoniam, 2016b). Quercetin decreased oxidative stress, NF-kappaB activation and iNOS over expression in liver of streptozotocin-induced diabetic rats. It is believed to protect against several degenerative diseases by preventing lipid peroxidation.

Other activities: Quercertin helps regeneration of β-cells and increases insulin release in streptosotozin-diabetic rats. Insulin release was enhanced by approximately 44-70 folds when isolated rat islets were exposed to quercetin (0.01-0.1 mmol/l). Further, it enhances glucose uptake by isolated β-cells and inhibits glucose production in rat liver slices. Quercetin protected rats from streptozotocin-induced oxidative stress and β-cell damage. In a recent study, quercetin induced insulin secreation by direct activation of L-type calcium channels in pancreatic β-cells in culture. Quercetin and quercetin glycosides inhibited AGEs formation. Besides, quercetin inhibited aldose reductase (Subramoniam, 2016b). Quercetin has been reported to be effective in arteriosclerosis, bleeding, allergy and swellings. It is also known to be associated with reduced risk of certain types of cancers (Subramoniam, 2016b).

Limitations: The major problem associated with the use of quercetin is the very low *in vivo* bioavailability. However, the degree and method of quercetin's absorption *in vivo* has yet to be absolutely determined. It is thought that the predominant glucoside form is converted to the aglycone, which is then converted to one of several quercetin metabolites. Therefore, *in vitro* studies may not fully reflect *in vivo* effects.

6. β-Sitosterol

This is a phytosterol present in food stuffs such as cashew fruits, rice bran, wheat germ, peanuts, soybean and pumpkin seeds. Chemical structure of β-sitosterol is shown in Figure 5.

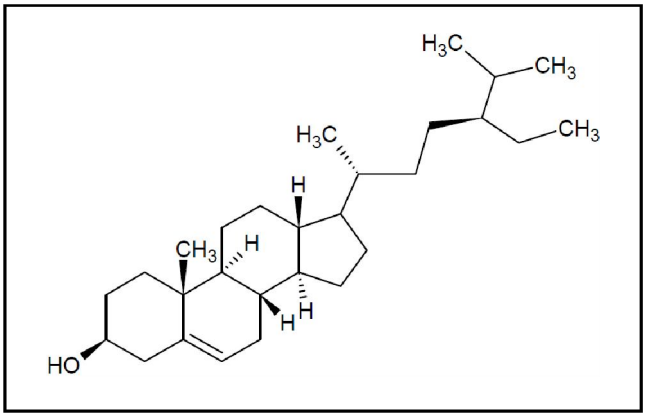

Figure 5: Structure of β-sitosterol

β-Sitosterol exhibits promising anti-oxidant and anti-inflammatory properties. It inhibited caraageenin-induced paw edema in rats; besides, it markedly reduced inflammation induced by cotton pellet-granuloma in rats (Subramoniam *et al.*, 2013).

Other activities: β-sitosterol helps in the regeneration of β-cells and insulin release from β-cells. Oral treatment with β-sitosterol increased the fasting plasma insulin levels and decreased fasting glycemia in rats. In addition, β-sitosterol improved the oral glucose tolerance with an increase in glucose-induced insulin secretion. Further, β-sitosterol treatment increased pancreatic antioxidant levels with a concomitant decrease in thiobarbituric acid reactive substances. β-sitosterol has been associated with cardiovascular protection, exerting its effect mainly through increasing the antioxidant defense system and effectively lowering the serum cholesterol levels in humans (Subramoniam, 2016b).

6. Conclusion

Arthritis is one of the major diseases and it is heartening to note that this disease can be prevented and/or controlled, to a large extent, with the use of specific plant food items as ingridients of diet to the required amount regularly. Edible parts of plants with anti-arthritis properties which are consumed as ingredients of diet by humans could be safe without the adverse effects of currently used non-steroidal anti-inflammatory drugs and immune-suppressors. Plants with antiarthritic properties in their edible parts include *Camellia sinensis* leaf, *Cinnamomum verum* bark (spice), *Coriander sativum* seed, *Curcuma longa* rhizome (spice

and an ingredient of many dishes), *Daucus carota* tuberous root (vegetable), *Mangifera indica* fruit peel and unripe fruit, *Piper nigrum* fruit (king of spices), *Piper longum* fruit (spice), *Punica granatum* fruit, *Syzygium cumini* fruit (black berry or black plum), *Trigonella foenum-graecum* seed (spice and an ingredient of many dishes), and *Zingiber officinale* rhizome. Since arthritis condition exhibits inflammation of joints, pain, oxidatiove stress and hyper-immune reactions (particularly in the case of rheumatoid arthritis), plant food with high levels of one or more of these properties and traditional use to treat arthritis are considered in this review as antiarthritic food plants. Other pharmacological properties of these food stuffs are also provided for proper understanding of their use as food medicines/nutraceuticals. Pure chemical entity nutraceuticals with anti-arthritis properties include chlorophyll-a and its degradation products, curcumin, epicatechin, mangiferin, quercetin and β-sitosterol. These compounds (nutraceuticals) or food stuffs containing these compounds (also known as nutraceuticals) can be judiciously used considering their mechanisms of action, if known. The mechanisms of action of some of the nutraceuticals mentioned above are known. For example, the anti-inflammatory mechanism of curcumin includes inhibition of cyclo-oxygenases and lipoxygenases; chlorophyll-a and its degradation products exhibit antiarthritis action primarily by the inhibition of TNF-α production. Further, studies are required in most of the cases to determine the amount to be consumed for better efficacy. At any rate, proper use of antiarthritic food stuffs (applying additional focused research results) is useful for improving the health of arthritic patients.

Conflict of interest

I declare that I have no conflict of interest.

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