

Tar Free White Paper

Mulethi (*Glycyrrhiza glabra*)

Tulsi (*Ocimum Sanctum*)

Triphala (Amalaki (*Emblica officinalis*), Bibhitaki (*Terminalia bellirica*), and Haritaki (*Terminalia chebula*))

Haldi(*Curcuma longa*)...

Lasun (*Allium sativum*)

Manjitha(*Rubia cordifolia*)

Shikakai(*Acacia concinna*)

Trikaatu (*Piper Longum, Zingiber Officinale, Piper nygrum*)

Mulethi (*Glycyrrhiza glabra*)

Glycyrrhiza glabra is a member of the Fabaceae family. It is commonly known as liquorice, licorice. It is a traditional plant, to which multiple health benefits have been attributed and its medicinal uses have been dated throughout the centuries. Liquorice is a perennial plant with a height of 0.7-2.0 m and erect growth. The roots of the plant are more than 1m deep. The root system consists of well-developed horizontal stolons and rhizomes. The bark of the roots and rhizomes has a brownish green to dark brown colour. Glycyrrhizin, the main bioactive compound of liquorice roots, is used as sweetener, with its taste being 50 times sweeter than sugar. Moreover, liquorice extracts can be used as flavouring agents in baked foods, alcoholic beverages and chewing gums. Example:-0.15% for non-alcoholic beverages, herbs and seasonings and plant protein products. 0.5% liquorice extracts are used for vitamins and mineral dietary supplements. Among the alternative uses of liquorice biomass, bioenergy production, pulp production and the application of liquorice processing by-products as fertilizers, are also included. Scientists have proposed the use of liquorice in processing industry waste as an organic substrate that could minimize the use of fertilizers in strawberry cultivation(1).

Moreover, 15 different saponins and 49 phenolic compounds (including their glycosides) have been already identified in liquorice roots. Among the most commonly known macronutrients, liquorice roots present a substantial amount of sugar between 8.10% to 9.30%) and ash between (4.58% to 7.40%). Various raw polysaccharides (RPS) derived from the aqueous extract after ethanol precipitation, contained a substantial amount of proteins 19% and 81% of carbohydrates, mainly arabinose, galactose, glucose and glucuronic acid (1).

Glycyrrhizin is one of the most studied chemical constituents derived from the roots of *G. glabra*. Liquorice is well known for its multiple ethnopharmacological applications, including its uses as anti-inflammatory, antiulcer, antibacterial, antifungal, antiviral, anti-allergic and immunostimulant. Liquorice is also used as a prescription drug for the treatment of various diseases in Japan in various forms [e.g. injectable preparations (Stronger Neo-Minophagen® C)

or tablet(Glycyron®)] while more than 71% of traditional Japanese Kampo medicines contain liquorice with an allowed minimum content of 2.5% for glycyrrhizin. Liquorice extracts are also ingredients of various drugs in many countries, while glycyrrhetic acid 3- β -O-hemisuccinate (carbenoxolone), a derivative of glycyrrhetic acid, is being used as a prescription drug.

Bioactive Effect and Physiological action are (1) :-

Antibacterial -Suppression of the adhesion of Helicobacter pylori to human gastric mucosa

Anticariogenic -Antibacterial activity against Streptococcus mutans causing dental caries.

Antifungal - Reduction/inhibition of the yeast (Candida albicans)

Growth - Inhibition of the biofilms formation/growth

Anti Inflammatory -Inhibition of nitric oxide (NO), and prostaglandin E2 (PGE2) production

- Inhibition of inflammatory cytokines production (i.e.tumor necrosis factor- α (TNF- α), interleukin 1 β (IL-1 β),interleukin-6 (IL-6)).

- Inhibition of reactive oxygen species (ROS) production-Reduction of inflammatory proteins production (i.e. cyclooxygenase-2 (COX-2))

Antioxidant - Inhibition of reactive oxygen species generation.

- Inhibition of mitochondrial lipid peroxidation.

- Reduction of the NADPH oxidase activation and increase of cellular glutathione.

Antiprotozoa- Alteration of the ultrastructure of the parasite mitochondria.

-Inhibition of Pf LDH (Parasite lactate dehydrogenase) enzyme acting at NADH site.

-Induction of oxidative stress in parasites through ROS (Reactive Oxygen Species) /RNS(Reactive Nitrogen Species) generation.

Antitumor - Protection against oxidative damage induced by hydrogen peroxide (H₂O₂)

-Inhibition of tumor cells proliferation and migration

- Inhibition of cyclooxygenase (COX)-2 overexpression

- Suppression of the activity of phosphoinositide 3-kinase (PI3K)

-Inhibition of tumor cell growth and migration via blocking AKT (serine-threonine protein kinase)/mTOR(mammalian target of rapamycin)/STAT3 (signal transduction and activator of transcription) pathway

Antiulcer - Inhibition of adhesion of Helicobacter pylori to human gastric mucosa

Antiviral - Inhibition of virus attachment process and replication

- Inhibition of infectious virus particles release

Physiological effects

- Cardiovascular - Reduction in the atherosclerotic lesions.

-Inhibition of LDL(low-density lipoprotein) oxidation

-Action as thrombin inhibitor

- Decrease in tube formation in vascular endothelial cells.

- Modulation of vascular injury and atherogenesis.

-Protection against the development of arrhythmia Cerebral/ Nervous.

- Inhibition of serotonin re-uptake.

- Memory enhancing effects.
- Increase of succinate dehydrogenase (SDH) activity in several parts of the brain
- Improvement of brain energy supply.
- Amelioration of the effect of vibration.

Endocrine - Reduction of the glucose levels

- Increase in antioxidants enzyme activity in pancreas
- Action as natural estrogen agonists
- Inhibition of tyrosinase activity

Immune -Action against immune function dysfunction

- Improvement of antioxidant defense system.
- Activation of immune cells-Stimulation of the expression of CD69 glycoprotein on granulocytes and NK (Natural killer) cells
- Enhancing of dendritic cells maturation
- Regulation of iNOS expression

Hepatic - Protection against oxidative stress of the liver

- Reduction of liver enzyme levels
- Changes in antioxidant enzymes (SOD: superoxide dismutase and CAT: catalase) activities in the liver
- Inhibition of hepatic lipid peroxidation
- Protection of liver mitochondria against oxidative stress

Renal - Anti-nephritis effects

- Ameliorates renal defects

Respiratory - Antitussive effects

Tulsi (*Ocimum Sanctum*):

Tulsi has been used in Ayurveda medicine for thousands of years. It is referred to as “the Queen of Herbs”. Tulsi is one of India’s most sacred herbs. Tulsi has been cultivated in India for over five thousand years and has been included in key historical documents including the Rigveda , in traditional Indian medicine known as “Caraka Samhita” (discovered around 1500 BC); along with the Nighantu Adarsha, another historic medical text. In all cases, it was found that Tulsi was one of the top medicinal herbs used in ancient times. This plant represents harmony, serenity, purity and good fortune and due to its spiritual significance [2].

Tulsi is a bushy shrub that grows to about 18 inches in height. Its leaves are oval and serrated with colors ranging from light green to dark purple, depending on the variety. Tulsi is loaded with antioxidants, which are powerful nutrients that protect the body from free radicals and prevent oxidative cell damage [2].

Tulsi's unique chemistry is very complex but offers benefits considered beyond that offered from other herbs. Tulsi contains hundreds of phytochemicals containing health-promoting properties. Tulsi's active constituents include eugenol, , cinnamyl acetate and beta-elemene. The synergies offered by the phytochemicals found in Tulsi contain potent antioxidant, adaptogenic and immune enhancing benefits that fight stress, promote better health and also the following [2]:

- Supports and builds immune system
- Improves digestive system, boosts healthy metabolism
- Increases sense of calm as it relieves stress due to its adaptogenic properties;
- Contains anti-aging properties
- Helps maintain normal blood sugar levels
- Skeletal joint support
- Helps to maintain normal cholesterol levels
- Relieves insect bites;
- Treats ringworm and other skin disorders;
- Anti-parasitic
- Fights malaria and various forms of poisoning
- Enhances stamina and stimulates energy
- Mood stabilizer
- Tonic for nerves
- An agent to strengthen the stomach and rid toxins from the body

Other Benefits:

Chewing the leaves of Tulsi can cure many types of fevers. Tulsi can prevent malaria and dengue fever; a decoction of Tulsi can reduce the body's temperature associated with a high fever. As a germicidal agent and disinfectant, Tulsi protects against many forms of viral infections. Tulsi leaves offer a rich supply of essential oils including eugenol, nerol, camphor and a variety of terpenes and flavonoids. Tulsi contains antibiotic compounds that show a lowering effect on blood pressure [2].

Specifically, two water soluble flavonoids found in Tulsi— orientin and vicenin protect cell structures and protect chromosomes from radiation and oxygen-based damage. A number of studies on animals have shown that Tulsi protects healthy cells from the toxicity associated with chemotherapy and radiation. Studies have also shown that Tulsi influences the neurochemistry of the brain similar to antidepressant meds but without the harmful toxic effects prevalent in pharmaceutical medications. Leaves of Tulsi (*Ocimum sanctum*) to have highly significant hepatoprotective properties [2].

Cough and Respiratory Ailments:

Chewing Tulsi leaves helps fight coughs and flu and mobilizes bronchitis and asthma attacks. A decoction of leaves, honey and ginger is a remedy effective against bronchitis, asthma, colds and flu and a decoction of leaves, cloves and Himalayan pink salt also relieves flu symptoms. Sipping and/or gargling Tulsi leaves gently boiled in water can help relieve the discomforts of sore throats. Tulsi is an important ingredient in cough syrups and expectorants [2].

Heart Disorders:

Tulsi contains Vitamin C and other anti-oxidants such as eugenol, and camphene, and is very beneficial in fighting heart disease and the associated weakness it causes. Studies also show that the eugenol component can block the activity of an COX enzyme in the body. Many over the counter NSAIDS medications including aspirin, ibuprofen and acetaminophen also work by inhibiting this same enzyme. Since Tulsi has this same, albeit safer, enzyme inhibiting effect, it qualifies Tulsi as a very important “anti-inflammatory” Tulsi can also reduce cholesterol levels and blood pressure and protect the heart from harmful free radicals [2].

Anti-cancer:

Neutralizes bio-chemicals known to contribute to cancer, Tulsi also restricts the blood vessels that feed tumors. It also inhibits the growth in oral cancer caused by tobacco [2].

Headache:

Powdered leaves mixed with sandalwood to form a paste and applied to the forehead is an effective relief from headaches [2].

Liver Support:

Improves the metabolic breakdown and elimination of toxic chemicals in the blood, and therefore counteracts various liver disorders and contributes to a healthy functioning liver [2].

Nutrition:

Contains vitamins C and A, along with iron, zinc, calcium and chlorophyll and many other phytonutrients, Tulsi enhances an efficient digestive system while promoting so many other benefits [2].

Nutritional Composition of Tulsi per 100 Grams [2]**Compound**

Energy	23 Kcal
Carbohydrates	2.65 g
Protein	3.15 g
Total Fat	0.64 g
Cholesterol	0 mg
Dietary Fiber	1.60 g

Vitamins

Folates	68 µg
Niacin	0.902 mg
Pantothenic acid	0.209 mg
Pyridoxine	0.155 mg

Riboflavin	0.076 mg
Thiamin	0.034 mg
Vitamin A	5275 IU
Vitamin C	18 mg
Vitamin E	0.80 mg
Vitamin K	414.8 µg
Electrolytes	
Sodium	4 mg
Potassium	295 mg

Minerals

Calcium	177 mg
Copper	385 mg
Iron	3.17 mg
Magnesium	64 mg
Manganese	1.15 mg
Zinc	0.81 mg

Phyto-nutrients

Carotene-β	3142 µg
Crypto-xanthin-β	46 µg
Lutein-zeaxanthin	5650 µg

Tulsi is a rich source of Vitamins, Electrolytes, Minerals and Phyto-nutrients. All this combination acts as an immune booster that gives Tulsi a unique ability to fight for viral infections and along with this its antipyretic nature is what we believe is helpful in combating the Covid-19 [2].

Triphala

Triphala is a well known polyherbal formulation from Ayurveda. It is a Rasayana Drug used in Indian System of Medicine (ISM)¹. Triphala is a mixture of three fruits which is composed of dried fruits of *Emblica officinalis* Gaertn (Euphorbiaceae), *Terminalia bellerica* Linn (Combretaceae) and *Terminalia chebula* (Combretaceae) in equal proportions (1:1:1) as described in Ayurvedic Formulary of India [3].

It is used as colon tonic, laxative, eye rejuvenator, anti-inflammatory, antiviral etc. Triphala has been tested as an antioxidant and also radioprotector in mice. Triphala is employed to treat conditions like headache, dyspepsia, ascites and leucorrhoea. It is also used as a blood purifier that can improve mental faculties and possess anti-inflammatory, analgesic, anti-arthritic hypoglycemic and anti-aging properties. Triphala is claimed to have antiviral and antibacterial effect. Triphala is prescribed for various symptoms of infections, fatigue, assimilation and infectious diseases such as tuberculosis, pneumonia, AIDS, periodontal diseases. It is reported to reduce considerably the damage due to oxidative stress. Triphala inhibits the growth of Gram

positive and Gram negative bacteria. Triphala is rich in gallic acid, Vitamin C, ellagic acid, chebulic acid, bellericanin, β -sitosterol and flavonoids [3].

Phenolic acids, flavonoids and tannins are the most commonly found polyphenolic compounds in the plant extracts [3].

Triphala contains $38\pm 3\%$ polyphenols and $35\pm 3\%$ tannins. Triphala contains sufficient gallic acid [3].

Triphala as an anticancer drug

Triphala possesses cytotoxic effect on cancer cell lines. Gallic acid is the major component and suppression of growth of cancer cells may be due to gallic acid. Viability of breast cancer cells (MCF-7) decreased when treated with increasing concentration of triphala. Cytotoxicity of normal breast epithelial cells was not affected when treated with similar concentration of triphala. Triphala induces cytotoxicity in tumor cells but not in normal cells. Triphala inhibits the growth of human pancreatic cancer cells in cellular and in vivo models. Triphala possesses radioprotective effects and delays the onset of mortality [3].

Antioxidant Activity of Triphala:

Polyphenolic contents in triphala are responsible for the antioxidant and radio protecting ability, reduce the oxidative stress by converting reactive oxygen free radicals to non-reactive products. Triphala significantly prevents cold-stress induced oxidative stress. Cold stress induced oxidative stress is measured by Lipid Peroxidation (LPO), enzymatic Superoxide Dismutase (SOD), Catalase (CAT), non-enzymatic (Vitamin C) antioxidation status. Administration of Triphala (1g/Kg/body weight/48 days) prevents Cold Stress induced oxidative stress and elevation in LPO and Corticosterone levels. The antioxidant property can be correlated to prevention of cold stress induced oxidative stress. Triphala and the individual ingredients of triphala effectively inhibit γ -radiation induced strand break formation in plasmid DNA. They inhibit radiation induced radicals like DPPH and superoxide. Triphala also inhibited uric acid formation [3].

Triphala against Stress:

Triphala supplementation has a protective effect against stress. Triphala administration for 48 days (1g/kg/animal body weight) prevents cold stress induced behavioral and biochemical abnormalities like increase in immobilization, with decrease in rearing, grooming and ambulation behavior, significant increase in lipid peroxidation (LPO) and corticosterone levels [3].

Antimicrobial Activity of Triphala

Triphala controls dental plaque, gingival inflammation and microbial growth caused by Streptococcus mutans and Lactobacillus. Triphala controls plaque from baseline and its activity is comparable to commonly available mouthwash Chlorhexidine. Ayurvedic formulations like

Triphala Mashī exhibit antimicrobial activity attributed to phenolic compounds and tannins in triphala [3].

It inhibits dose dependent growth of gram positive and gram negative bacteria. Triphala and its individual fruit components have a potent antibacterial action against a wide spectrum of bacterial isolates like *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Shigella sonnei*, *Staphylococcus aureus*, *Vibrio cholera*, isolated from HIV infected patients. Aqueous extract has activity against *S. epidermidis*, *S. aureus*, *P. vulgaris*, mildly antibacterial against *S. typhimurium*, *B. subtilis* and negligible/ no inhibitory effect against *E. coli* and *E. aerogenes*. The three fruits constituting triphala show potent antibacterial activity against *E. coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Staphylococcus epidermidis*, *Salmonella typhi*, *Salmonella typhimurium*, *Enterobacter aerogenes* [3].

Triphala in wound healing

The ointments prepared from triphala extracts show significant wound closure in vivo. The granulation tissue shows reduced bacterial count, increase in collagen, hexosamine, uronic acid. Collagen sponges incorporated with triphala when used to close wounds showed increased thermal stability, water uptake capability, faster wound closure, improved tissue regeneration. Epigallocatechin gallate interaction with collagen contributes to this quick wound healing activity [3].

Triphala as an immunomodulator

Triphala has an immunomodulatory activity when tested using carbon clearance test and Delayed Type Hypersensitivity (DTH) [Foot Pad Swelling] response. Triphala Mega extract when administered at 500 mg/Kg and 1000 mg/Kg orally showed an increase in carbon clearance index which reflects enhancement of phagocytic function of mononuclear macrophage and nonspecific immunity. There was an increase in DTH response or cell mediated immunity. Triphala mega extract had a stimulatory effect on T cells. The good immunomodulatory property of triphala could be attributed to flavonoids, alkaloids, tannins, saponin glycosides and phenolic compounds [3].

Triphala as anti-inflammatory:

Triphala when topically administered prevents uveitis induced by intravitreal injection of lipopolysaccharide from *Escherichia coli*. The inflammation of the anterior segment in control groups was significantly higher than in triphala treated groups. Triphala exhibits a protective effect in endotoxin-induced uveitis. The treated groups showed not only significant reduction in severity of clinical signs and also reduction in aqueous humor levels of inflammatory cell, protein content and TNF- α compared with that of the control group [3].

Triphala in Arthritis:

Triphala treatment inhibited paw volume, levels of lysosomal enzymes, lipid peroxidation and inflammatory mediator tumour necrosis factor- α , β -glucuronidase and lactate dehydrogenase

levels were reduced. Triphala exerted a strong anti inflammatory effect against gouty Arthritis [3].

Haldi (Curcuma Longa)

The medicinal properties of turmeric are widely accepted in modern medicine. Its role in wound healing, arthritis, inflammatory bowel disease, antioxidant property, and chemopreventive, bioprotectant, antimutagenic, anticarcinogenic, antimicrobial, antidiabetic, antithrombotic, antiangiogenic, and hepatoprotective properties are widely accepted [4].

It has clinical properties anti inflammatory activity, wound healing, and antioxidative, chemopreventive, antimutagenic, anticarcinogenic, antimicrobial, antidiabetic, antiangiogenic, antithrombotic, and hepatoprotective properties. It is also useful against gastrointestinal and respiratory disorders and arthritis [4].

The Principal Compounds in Turmeric:

The constituents are ar-turmerone, turmerone, zingiberene, and curone. The principal bioactive components of turmeric are named curcuminoids. These curcuminoids are a rich source of phenolic compounds. Turmeric consists of 3–5% curcuminoids, which include mainly curcumin I, curcumin II, and curcumin III. The active ingredient of turmeric is curcumin. Curcumin is the substance that imparts to turmeric most of its therapeutic properties. The rhizome is 70% carbohydrates, 7% protein, 4% minerals, a minimum of 4% essential oils, and about 1% resin. It also contains vitamins and other alkaloids [4].

Current research shows that about 98% of all diseases are controlled by a molecule called NF-kappa B, a powerful protein which promotes abnormal inflammatory response in the body. Excess of NF-kappa B can lead to cancer, arthritis, and a wide range of other diseases, and studies show that the curcumin subdues NF-kappa B, thus preventing nearly all diseases afflicting the human body [4].

Turmeric enhances the flavor of food, aids digestion (in particular, that of protein), promotes absorption of the digested material, and, in turn, regulates body metabolism. It helps to regulate intestinal microflora and is particularly recommended to be taken after a course of antibiotics, thereby reducing the risk of gastritis and ulcer formation in the intestines. In diabetics, turmeric lowers blood sugar. Because it contains natural cyclooxygenase inhibitors, it shows good anti-inflammatory action [4].

The antiinflammatory property is due to the capacity of turmeric to lower histamine levels, while possibly increasing production of natural cortisone by adrenal glands. It also helps both liver and gallbladder function. It has been shown to be helpful in the treatment of arthritis, rheumatoid arthritis, osteoarthritis, injuries, trauma, and stiffness both under normal activity and hyperactivity. It shows that natural cortisone production by the adrenal glands is enhanced. Its most important anti-inflammatory mechanism is based on its positive effects on the prostaglandins (PGs), a large family of potent lipids produced by the body. PG1 and PG3 calm the body, while PG2 inflames it. Turmeric is a potent inhibitor of cyclooxygenase,

5-lipoxygenase, and 5-HETE production in neutrophils, which reduces PG2 levels, resulting in reduced body pain and inflammation [4].

The Indian traditional medical systems use turmeric for wound healing, rheumatic disorders, gastrointestinal symptoms, deworming, and rhinitis and as a cosmetic. Studies in India have explored its anti-inflammatory, cholekinetic, and antioxidant potentials and its preventive effect on pre carcinogenic, anti inflammatory, and antiatherosclerotic effects in biological systems both under in vivo and in vitro conditions in animals and humans. Both turmeric and curcumin, the major bioactive principle in lending color to turmeric, were found to enhance detoxifying enzymes, prevent DNA damage, improve DNA repair, decrease mutations and tumor formation, and exhibit antioxidative potential in animals. Limited clinical studies suggest that turmeric can significantly impact excretion of mutagens in urine among smokers and help regress precancerous palatal lesions. It reduces DNA adducts and micronuclei in oral epithelial cells. It prevents formation of nitrous compounds both in vivo and in vitro. It delays induced cataract in diabetics and reduces hyperlipidemia in obese rats. Recently, several molecular targets have identified turmeric for therapeutic/preventive effects. Turmeric is also used to treat asthma, dysmenorrhea, psoriasis, eczema, arthritis, and hepatic and digestive disorders and to prevent and treat cardiovascular diseases [4].

Curcumin exhibits anti-inflammatory , antioxidant , antiviral , antimicrobial, anticarcinogenic , and antimutagenic properties protecting the body from mutagens such as smoke and other pollutants. Recent investigations suggest that curcuminoids are active in the external treatment of certain cancerous conditions, and this is presumably related to the cytotoxicity of these substances, which has been demonstrated on cell cultures, including tumor cells . Besides these, curcumin has a variety of potentially therapeutic properties such as antineoplastic, antiapoptotic, antiangiogenic, cytotoxic, immunomodulatory , antithrombotic, wound healing, antidiabetogenic, antistressor, and antilithogenic actions . Turmeric has been used in traditional Indian medicine for the treatment of jaundice and other ailments related to the liver, ulcers, parasitic infections, various skin diseases, sprains, inflammation of the joints, and cold and influenza symptoms and for preserving food stuff because of its antimicrobial properties [4].

Medicinal Properties of Turmeric

Anti-inflammatory Activity:

Turmeric in traditional medicine has been from India and China, especially for its immunomodulatory properties. Dendritic cells (DCs) are antigen-presenting cells specialized to initiate and regulate immunity. The ability of DCs to initiate immunity is linked to their activation status. The turmeric inhibit the activation of human DCs in response to inflammatory cytokines. These studies provide a mechanism for the anti-inflammatory properties of turmeric. However, they suggest that these extracts are not synergistic and may contain components with

mutually antagonistic effects on human DCs. Harnessing the immune effects of turmeric may benefit from specifically targeting the active fractions [4].

Wound Healing:

A central consideration in common medical practice has been the healing of irradiated wounds, because radiation disrupts normal response to injury, leading to a protracted recovery period. Pretreatment of irradiated wounds with curcumin was reported to significantly enhance the rate of wound contraction; decrease mean wound healing time; increase synthesis of collagen (the principal protein of connective tissues in animals), hexosamine, DNA, and nitric oxide; and improve fibroblast and vascular densities, indicating that curcumin pretreatment has a conducive effect on the irradiated wound and could be a substantial therapeutic strategy in initiating and supporting the cascade of the tissue repair process [4].

Arthritis:

Turmeric has been used for centuries in Ayurvedic medicine, as a treatment for inflammatory disorders including arthritis. The *in vivo* antiarthritic efficacy of an essential oil-depleted turmeric fraction has been attributed to the three major curcuminoids. Turmeric, a close relative of ginger, is a promising disease-preventive agent as well, probably due largely to its anti-inflammatory properties [4].

The clinical trial was carried out in Italy, for 3-months involving 50 patients, who were diagnosed through X-ray having osteoarthritis of the knee. Half of the participating patients took the turmeric formulation, in addition to standard medical treatment; those in the second group continued following their physicians' recommendations. After 90 days, the researchers found a 58% decrease in overall reported pain and stiffness in the knee joint, as well as improvement in physical functioning among the group of patients on turmeric formulation, compared to the controls. And blood tests showed a 16-fold decline in C-reactive protein, a marker for inflammation. Patients in the turmeric group were able to reduce their use of nonsteroidal anti-inflammatory drugs by as much as 63%, a remarkable improvement, compared with the other group. Turmeric may be effective in the prevention or treatment of colon, breast, and prostate cancer [4].

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is characterized by oxidative and nitrosative stress, leukocyte infiltration, and upregulation of proinflammatory cytokines. The protective effects of curcumin, an anti-inflammatory and antioxidant food derivative, for colitis in experimental animal were demonstrated by the significant reduction in the degree of neutrophil infiltration, lipid peroxidation in the inflamed colon, and the decreased serine protease activity. Curcumin also reduced the levels of nitric oxide (NO) and O₂ associated with the favorable expression of cytokines and inducible NO synthase. Thus, curcumin exerts beneficial effects in experimental colitis and may, therefore, be useful in the treatment of IBD [4].

Garlic (*Allium sativum*)

Allium sativum L. belongs to the member of the family *Alliaceae* and broadly used on the second number after onion use [5].

Chemical Composition:

Garlic is considered to be a monocotyledonous biennial plant, contains sulfur compounds providing nutraceutical and medicinal effects inclusive of aliin, allicin, ajoene, allylpropyl, diallyl, trisulfide, sallylcysteine, vinylidithiines, S-allylmercaptocystein, peptides, steroids, terpenoids, flavonoids, and phenols. It contains aliin which is easily metabolised into allicin by the help of enzyme allinase which is activated through injuries on garlic. Allicin is further metabolized to vinylidithiines. Besides the above mentioned sulfur compounds garlic consists of 17 amino acids and their glycosides, arginine and others. Minerals are also available such as selenium, germanium, tellurium and other trace minerals, and others. In addition garlic consists of arginine, oligosaccharides, flavonoids, and selenium, all of which may be beneficial to health [5].

Multiple benefits of garlic are [5]:

- Hypertension
- Reducing cholesterol levels
- Lowering blood sugar levels
- Decreasing cardiovascular risk
- Prevention of blood clotting
- Protection of the liver
- Antitumor properties
- Strengthening of immune system
- Stimulating the lymphatic system
- Active antioxidant to prevent free radical damage
- Antineoplastic properties
- Antimicrobial properties
- Nutritional value
- Seasoning and flavoring agent

Pharmacological Activities of Garlic:

Due to the presence of biological active component named as allicin and its derivative, garlic is widely used as a medicine to cure a wide range of diseases and conditions associated with heart and blood system that includes; high blood pressure, high cholesterol, coronary heart disease, heart attack, hardening of the arteries, etc. Research on garlic stated that it can be used for prevention of various types of cancer including colon cancer, rectal cancer, stomach cancer, breast cancer, prostate cancer and bladder cancer, and lung cancer. Moreover, it helps in treating various problems related to an enlarged prostate (benign prostatic hyperplasia; BPH) or diabetes or osteoarthritis or hayfever (allergic rhinitis) or traveler's diarrhea or high blood pressure late in pregnancy (pre-eclampsia) or cold and flu. Garlic has promising effect against treatment of asthma, arthritis, sciatica, lumbago, backache, bronchitis, chronic fever, tuberculosis, rhinitis, malaria, obstinate skin diseases which means in case of leprosy, leucoderma, discolouration of the skin and itches, indigestion, colic pain, enlargement of spleen, piles, fistula, fracture of bone,

gout, urinary diseases, diabetes, kidney stones, anemia, jaundice, epilepsy, cataract and night blindness [5].

Therapeutic and Pharmaceutical Use:

Garlic plays an important role in the area of pharmaceutical and widely used for the treatment of cardiovascular and other reasons causing ailments [5].

- **Antilipemic-** Reduces cholesterol biosynthesis by inhibiting HMG-CoA reductase and 14-alpha-demethylase
- **Antihypertensive-** Acts as a hypertensive agent, plays a significant role in reduction of systolic blood pressure (SBP) and diastolic blood pressure (DBP)
- **Antibiotic-** Broad spectrum antimicrobial agent (antibacterial, antifungal, antiparasitic, antiprotozoan, antiviral properties)
- **Anti-tumor Effects-** Inhibits development of cancer in the presence of known tumor promoters and sulphurous components present in garlic; Liable for avoiding cancerous cells development in the stomach, liver, and other organs of humans
- **Antimicrobial Activity-** Alternative form of treatment or prophylaxis in cases of infections especially gastrointestinal infections.
- **Anthelmintic-** Beneficial for treatment of intestinal worms and tapeworms
- **Diuretic-** Helps in getting rid of body liquids; beneficial in the treatment of rheumatism, gout, arthritis, hidropesía, edemas
- **Digestive-** Facilitates digestion by stimulating the liver, gallbladder and pancreas
- **Vaginal Infections-** Acts as bactericidal and fungicidal; responsible for correcting the infections caused by vaginal irritation, vaginitis or vaginal flow
- **Platelet Effects-** Inhibitory properties for platelet aggregation during the in vitro and in vivo studies; reduction of platelet-dependent thrombus formation and anti-platelet activity
- **Sickle Cell Anemia**
- **Liver Protective/Detoxification Effects-** Inhibition of both formation and bioactivation of liver carcinogenic nitrosamines ; checked the mutagenic effects of Aflatoxin B1
- **Antioxidative and Radioprotective Effects-** Protects white blood cells from radiation damage, liver cells from lipid peroxidation and vascular endothelial cells from oxidant injury; Enhances antioxidative enzyme systems in cells; Helps in scavenging hydrogen peroxide which inhibits the formation of TBA-RS (byproducts of lipid peroxidation- Thiobarbituric Acid Reactive Substances); Protection of heart from cardiotoxic, anticancer drug doxorubicin; Protection of kidneys from antibiotic gentamicin

Garlic acts as an effective agent to cure any type of problems and helps in fighting stress and fatigue, and maintain healthy bodily functions due to its wide nutritive value which can be easily studied from the below mentioned table.

Summary of Nutritive Value of Garlic [Source *USDA nutrition database (2009)*][5]

Substance	Amount found/100g	Substance	Amount Found/100 g

Water (Moisture)	58.58%	Vitamin B6	1.235 g
Energy	623 kJ (149 kcal)	Folate (Vitamin B9)	3 µg
Carbohydrates	33.06 g	Vitamin C	31.2 mg
Sugars	1.00 g	Calcium	181 mg
Dietary Fiber	2.1 g	Iron	1.7 mg
Fat	0.5 g	Magnesium	25 mg
Protein	6.39 g	Phosphorus	153 mg
Beta-carotene	5 µg	Potassium	401 mg
Thiamine (Vitamin B1)	0.2 g	Sodium	17 mg
Riboflavin (Vitamin B2)	0.11 mg	Zinc	1.16 mg
Niacin (Vitamin B3)	0.7 mg	Manganese	1.672 mg
Pantothenic Acid (Vitamin B5)	0.596 mg	Selenium	14.2 µg

Manjitha(Rubia cordifolia)

Rubia cordifolia is a flowering plant species. It is commonly known as manjistha. Roots and stems are an active part of the plant. Plant has many pharmacological actions like blood purifier activity, anticancer, astringent, anti-acne, antiinflammatory, anti-microbial, antidysenteric, antiseptic, nephroprotective, antirheumatic and hepatoprotective properties [6].

Phytochemicals

Different classes of bioactive compounds such as anthraquinones and their glycosides, naphthoquinones and glycosides, terpenes, bicyclic hexapeptides, iridoids, carboxylic acids (malic, citric, quinic, rosmarinic acids) and saccharides (xylose, ribose, fructose, glucose, sucrose, primverose) were isolated from various parts of *R.Cordifolia*. Saponins and some naphthene derivatives are also isolated. It contains alizarin, pseudoparapurins, rubuadin along with glucoside, lucidine, purpurin and manjisthin. Other compounds include Quinones,Iridoids,Bicyclic hexapeptides [6].

Traditional uses in different systems of herbal medicine

In the traditional **korean system of medicine**, the root is used to treat rheumatism, jaundice and menstrual disorders. In philippine system, a decoction of the root is drunk as a remedy for urinary disorders. The natives of the republic of south africa take a decoction of the leaf or root for pleurisy and other inflammatory conditions of the chest. The stem is used in tibetan system of medicine in the treatment of blood disorders and spreading fever of kidneys and intestines [6].

Unani system of medicine:- *R. cordifolia* has been prescribed for paralysis, dropsy, jaundice, amenorrhoea, urinary tract obstructions, skin disorders, menstrual disorders (excessive or painful bleeding), renal stone, urinary disorders and blood detoxification [6].

Chinese system of medicine:- roots help menstrual flow, promote blood circulation, promote urination, stop coughing blood or vomiting blood, nose bleeding. The plant is also useful in treatment of missing menses due to blood stasis, pain and inflammation caused by bleeding and blood circulation stasis, injuries from impacts and in jaundice and edema. The herb is internally used for abnormal uterine bleeding, internal and external haemorrhage, bronchitis, and rheumatism [6].

Ethnoveterinary usage:- *R. cordifolia* is used in the treatment of liver fluke, dysentery, maggots, wounds and intestinal worms in animals [6].

Pharmacological activity

Anti-acne property:

The anti-acne activity of anthraquinone rich fraction of *R. cordifolia* in a gel formulation against propionibacterium acne, staphylococcus epidermidis, malassezia furfur is proved when compared with standard clindamycin gel [6].

Anti-arthritic property:

The anthraquinones rich fraction of ethanolic extract of *R. cordifolia* has imperative anti-arthritic potential and showed edema inhibition in induced arthritic model, which is similar to a standard non-steroidal antiinflammatory drug, aspirin [6].

Anti-cancer property:

Anticancer activities of various fractions of *R. cordifolia* roots extracts were demonstrated through in vitro bioassays based on animal models. The crude aqueous extracts demonstrated growth inhibitory activity on selected cancer cell lines as well as on normal human mammary epithelial cells [6].

Anti-convulsant activity:

In modern medicine, *R. cordifolia* was reported to have anticonvulsant activity. Triterpenes inhibited seizures induced by maximum electric shock, electrical kindling and various chemoconvulsants in rats. Brain gaba and serotonin (5-HT) contents were raised by the compound proves its anticonvulsant property [6].

Shikakai(*Acacia concinna*)

Acacia concinna (Willd.) DC. (Fabaceae) is a climbing shrub and a well-known medicinal plant widely used in Southeast Asia. The leaves, bark and pods have been used as a herbal medicine for emetic, purgative and expectorant treatments. In addition, antioxidant, anti-coagulant, anti-platelet, anti-thrombotic, antidermatophytic and immune adjuvant activities are some of the valuable pharmacological properties of the plant [7].

Its seed has been used as folk medicine for Skin diseases [8].

Summary of the anti-obesogenic potential of the *A. concinna* [9].

Pancreatic Lipase Inhibition	High
Lipolysis Enhancement	Weak
Lipid Accumulation	Active (CD)
Reduction Toxicity	Positive

Almost every part of the plant is very useful. A decoction of the pods checks biliousness. Its decoction is a useful hair wash, promoting growth of hair, killing lice and removing dandruff.

The leaves are acidic] and are used in cooking as a substitute for tamarind. A paste (chutney) made of tender leaves, salt, tamarind and chillies is given in bilious affections such as jaundice. An infusion of the leaves is used in malarial fever; it checks flatulence and is a mild laxative [10].

The extracts of the leaves gave these to contain oxalic, tartaric, citric, succinic and ascorbic acids (7.4%), tartaric acid being the major constituent, amongst these. The leaves have also been found to contain the alkaloids, calycotomine (I, 1.2%) and nicotine (2.1%), the colouring matter, rutin (0.75%) and an enzyme, tartaric racimase. A new triterpenoid saponin has also been isolated from the leaves [10].

Various solvent extracts of pods of *Acacia Concinna* has alkaloids, flavonoids, Phytosterols, Saponins, Tannins, Phenolic compounds, Gum and Mucilage. The plant showed antibacterial activity against *Klebsiella pneumoniae*, *Bacillus Subtilis*, *E.coli*, *S.aureus*, *Pseuomonas aeruginosa*. It shows antifungal activity against *Aspergillus Niger*, *Candida albicans*, *Penicillium sp.* [11].

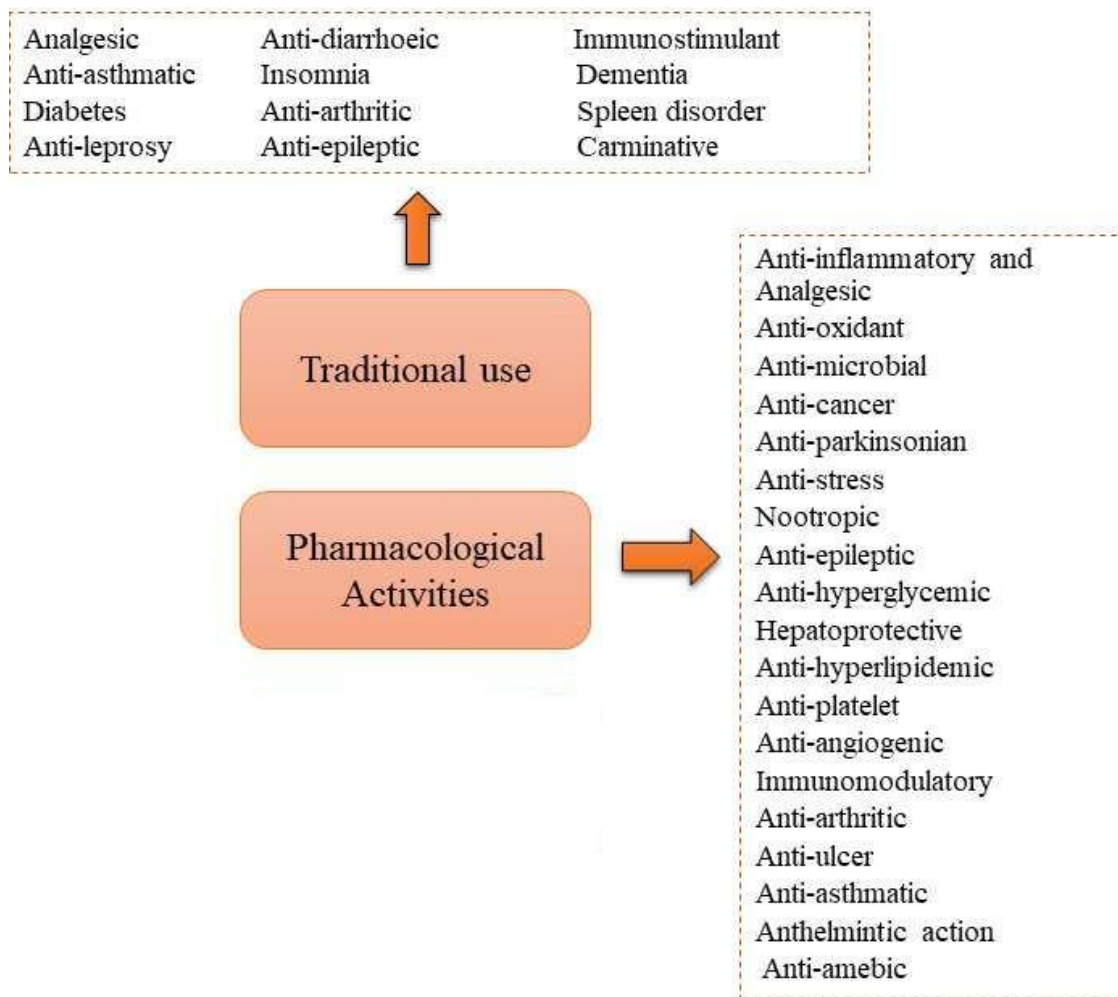
The leaves of *A. concinna* have been used to prevent diabetes and skin diseases in Myanmar, India and Thailand. Extract of *A. concinna* and its components could be effective for the development of agents for anti-thrombosis [12].

Antidermatophytic activity of pods of *Acacia concinna* commonly known as 'Shikakai' was studied against *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton violaceum*, *Microsporum nanum* and *Epidermophyton floccosum* [13].

Trikaatu (*Piper Longum*, *Zingiber Officinale*, *Piper nigrum*)

Piper longum:

Piper longum, commonly referred as 'Pippali', has found its traditional use in India, Malaysia, Singapore and other South Asian countries as an analgesic, carminative, anti-diarrhoeic, immunostimulant, post childbirth to check postpartum hemorrhage and to treat asthma, insomnia, dementia, epilepsy, diabetes, rheumatoid arthritis, asthma, spleen disorder, puerperal fever, leprosy etc. Many phytochemicals have been identified till date, including alkaloids as its major secondary metabolites (piperine and piperlongumine), essential oil, flavonoids and steroids. These exhibit a wide range of activities including anti-inflammatory, analgesic, anti-oxidant, anti-microbial, anti-cancer, anti-parkinsonian, anti-stress, nootropic, anti-epileptic, antihyperglycemic, hepatoprotective, anti-hyperlipidemic, anti-platelet, anti-angiogenic, immunomodulatory, anti-arthritic, anti-ulcer, anti-asthmatic, anthelmintic action, anti-amebic, anti-fungal, mosquito larvicidal and anti-snake venom [14].



Ayurvedic Pharmacopeia has mentioned the use of *P. longum* fruit in abdominal pain, phantom tumor, bronchitis, abdominal disease, rheumatism, leprosy, fever, spleen related disorders and in parasitic infection, while *P. longum* stem and root is indicated in flatulence, phantom tumor, ascites and abdominal enlargement. Also, in folklore medicine, *P. longum* is reputed for treatment of asthma, bronchitis, dysentery, pyrexia and insomnia. The utility of *P. longum* is mainly because of the piperine content, which itself possesses a diverse range of pharmacological actions. *P. longum* is used in 135 Ayurvedic formulations as reported [14].

The ancient verse of Ayurveda suggests the action of *P. longum* as bioenhancer and helps in removal of endotoxins from the body. The main part of *P. longum* utilized for medicinal purposes involves fruit and root [14].

Pharmacological Reports:

Anti-inflammatory Analgesic:

The textbooks from Indian origin have mentioned the use of *P. longum* fruits as analgesic and anti-inflammatory, specifically used locally for muscular pain. In this context, one of the study suggests that the extract of *P. longum* might act through the supraspinal pathway and provides relief in pain, though the dose used in this experiment seems impracticably high without accompanying any toxicological studies. The extract further repressed microsomal lipid peroxidation, suggesting that the inhibition of CAM and NF-kB may be mediated through inhibition of free radical generation in the form of lipid peroxidation [14].

Anti-oxidant:

Anti-oxidant agents are those which decline the oxidative stress and slackens the frequency of pathological circumstances instigated by oxidants. Oxidative stress is harmful to the cellular organizations as they cause peroxidation of lipid membrane consequent damage to membrane integrity and cell death, denaturation of proteins comprising enzymes, ion channels and strand breakage in DNA. These cellular changes clearly indicate that escalation of oxidants in the body leads to ailments like atherosclerosis, stroke, diabetes, Alzheimer's disease and cancer. The occurrence of phenols, flavonoids, and terpenes in plants make them better antioxidant agents, which are not only economic but also diverse and produce action without side effects [14].

Anti-microbial:

Extracts of *P. longum* showed anti-microbial activity against *Staphylococcus albus*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus megaterium* and *Aspergillus niger*. *P. longum* also seem to produce action against bacterial strains like *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Micrococcus flavus*, *Bacillus cerus*, *Bacillus subtilis*, *Klebsiella aerogenes*, *Klebsiella pneumonia*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus typhrium*, *Proteus mirabilis*, *Proteus vulgaris* [14].

Anti-cancer:

Due to the presence of multiple phyto-constituents in herbs, they provide protection against cancer through various mechanisms. Some of them involve (a) reducing oxidative stress, (b) reducing inflammation and depression in inflammation-associated pathways, (c) influencing phase I and II metabolism enzymes, and (d) anti-tumorigenic mechanism like modulation of transcription factors, antiapoptotic proteins, proapoptotic proteins, protein kinases, cell cycle proteins, cell adhesion molecules and growth signaling pathways. Extract of *P. longum* produces selective apoptotic cell death of malignant cells by directing the changes in mitochondrial membrane potential, following a nongenomic approach [14].

Anti-parkinsonian:

Parkinson's disease (PD) is progressive neurodegenerative movement disorder. The loss of dopaminergic neurons in the substantia nigra pars compacta (SN-pc) is considered a major underlying pathological event. This further results in motor disturbances and formation of Lewy bodies pathology. The efficacy of this plant to be used in PD was also supported by Bi et al., using MPTP model. The study revealed that the anti-oxidant levels were brought to normal values.. The protective effect of *P. longum* for dopaminergic neurons against inflammation-mediated damage was also studied [14].

Anti-stress:

The presence of phenolic compounds, tetracyclic triterpenes and fatty acid in plants make them appropriate as adaptogens. Adaptogens serve as tonics and are indicated in stress, neurological and psychological disorders. Pharmacologic assessment of adaptogens involves exposure to altered environmental surroundings, radiation, toxic substances, starvation, fear, and chronic diseases. Also, the most important feature of adaptogens is the ability to increase resistance to both physical and emotional stress. *P. longum* has also been evaluated for combating stress. Stress production in the body leads to alteration of normal physiology and is involved in various diseases like diabetes mellitus, hypertension, depression, anxiety, immunosuppressant etc. Stress also leads to the formation of free radicals and produces damage to neuronal cells. Mainly, the plants having adaptogenic action are suggested to provide relief under stressed conditions. Anti-stress activity of *P. longum* is attributable to combating the stimulation of hypothalamus pituitary adrenal (HPA) axis in stressful condition [14].

Nootropic:

Nootropic is a term utilized for therapeutic medications or supplements that positively affect cerebrum function[14].

Anti-hyperglycemic:

Inhibition of α -glucosidase and acarbose enzyme by *P. longum* extract seems to be the foremost fundamental mechanism for anti-diabetic property. *P. longum* extract being able to produce significant changes in these markers might help in combating diabetic symptoms and also associated comorbidities like diabetic retinopathy [14].

Hepatoprotective:

The protective action of *P. longum* has been demonstrated in CCl₄ induced liver fibrosis model. CCl₄ has been found to induce hepatic toxicity by metabolic activation. It is being converted to CCl₃ free radical by cytochrome P450 in endoplasmic reticulum. This free radical generation causes lipid peroxidation, demolition of Ca²⁺ homeostasis and cell death. Thus, it selectively serves as a good model to study liver toxicity. The in vivo hepatoprotective action of *P. longum* has also been validated by producing AlCl₃ induced liver toxicity. This metal induced toxicity was reversed by *P. longum* extract and the action ought to be due to anti-oxidant effect. The flavonoids present in the *P. longum* seem to be responsible for hepatoprotective action [14].

Anti-hyperlipidemic:

Experiments conducted to validate the action of *P. longum* involve assessment of lipid markers in blood suggesting its beneficial effect in case of hyperlipidemia[14].

Anti-platelet:

Extract from *P. longum* produce its inhibitory effect on platelet aggregation as a TXA₂ receptor antagonist. The study holds advantage in terms of involving various solvents to prepare extracts of *P. longum* and has demonstrated concentration dependent response, although part of the plant for the extract preparation was not mentioned [14].

Anti-angiogenic:

Angiogenesis is the process of formation of new blood vessels and is indicated in tumor metastasis. Anti-cancer treatment is gaining interest for angiogenic therapy due to low toxicity, extensive effectiveness, and the target that the neovasculature endothelial cells are genetically stable and implausible to advance acquired resistance. *P. longum* has a novel molecular mechanism that restricts the mutual angiogenic signaling pathways [14].

Immunomodulatory:

Immunotherapy is characterized as the way to deal with malignant growth by producing or enlarging a safe reaction against it. Immunomodulators are holding prominent promise for their utility in clinical aspects, as they can be used with chemotherapy and may provide additional benefits. The immuno-modulatory action of alcohol extract of *P. longum* when evaluated in mice, resulted in increment of the leukocyte count, bone marrow cellularity, α - esterase positive cells and total antibody production. These results suggest that immunomodulatory activity of *P. longum* may be due to the combined action of humoral and cell-mediated immune responses [14].

Angiotensin converting enzyme (ACE) inhibitor:

ACE is responsible for converting angiotensin I to angiotensin II, which is a potent vasoconstrictor. ACE inhibitors lessen the movement of the renin-angiotensin-aldosterone framework (RAAS) as the essential etiologic occasion in the advancement of hypertension in individuals with diabetes mellitus, as a feature of the insulin-obstruction disorder or as a sign of renal illness. *P. longum*, being traditionally recommended for cardiovascular disease, was evaluated for ACE inhibitory activity [14].

Anti-arthritis:

Rheumatoid arthritis (RA) is chronic auto-immune disorder that mainly affects joints and results in painful and swollen synovial tissue. The pathogenesis of RA includes synovial cell multiplication, angiogenesis, pannus development and cell insusceptible actuation by T cells, B cells and macrophages, which consequently leads to deformation in ligament and bone disintegration. The aim of the treatment is to suppress the pain and inflammation [14].

Anti-asthmatic:

National asthma campaign has reported that 60% of case of moderate asthma and 70% cases with severe asthma rely on alternative medical therapy. The use of *P. longum* for bronchitis and asthma has been mentioned in Ayurvedic formulation. In one experiment, it was postulated that the extract is active against type I allergic disorder due to its ability to prevent the release of allergic mediators from mast cells. In another study, *P. longum* fruit extract at the dose of 200 mg/kg, show bronchorelaxation with 83% preventive action in histamine-induced bronchospasm model of Guinea pig. Also, the anti-histaminic and anti-inflammatory action of *P. longum* have been postulated for preventive action towards asthma [14].

Anthelmintic:

Parasitic worms are referred to as helminths, which belongs to the class of flatworm (platyhelminthes) and nematodes (roundworms). The parasitic infection caused by these flukes and worms have become a major health problem throughout the world. These parasites cause

haemorrhage and connective tissue expansion at the site of connection, vacuolar degeneration in liver and hyperplasia in bile channel, accordingly, truly influencing wellbeing and efficiency of contaminated creatures. The use of *P. longum* as anthelmintic has been reported in Ayurvedic Pharmacopeia. Thus, *P. longum* provides a multi target approach for treatment of helminthic diseases and can provide a better formulation as anthelmintic. Nevertheless, efficient in vivo models need to be established for evaluation of the efficiency and toxicity of *P. longum* [14].

Anti-amebic:

Infection of human gastrointestinal system by *Entamoeba histolytica* is termed as amebiasis. *E. histolytica* is a protozoan parasite which attacks the intestine mucosa and spreads to vital organs in body. The action of *P. longum* fruit and root was evaluated, considering that it has been traditionally used for intestinal disorders. *P. longum* possesses high efficiency for treatment of amoebiasis [14].

Anti-fungal:

Dermatophytosis, commonly termed ringworms, is caused by fungal infection referred as dermatophytes. Dermatophytes are the group of closely related fungi which have the capacity to invade keratinized tissue like skin, hair and nails. These infections are cutaneous and do not invade soft tissue, however, the infections are posing major health issues in the world. These species producing cutaneous infections are also referred to as keratinophilic mycoflora. As the available antifungal drugs are producing serious side effects, thus, there is need for alternative therapy. Das et al., has performed sequential extraction of leaves of *P. longum* wherein chloroform and methanol extract were effective against *Trichophyton mentagrophytes*, *T. rubrum*, *T. tonsurans*, *Microsporum fulvum* and *M. gypseum*, serving as a compelling phytotherapy against dermatophytes [14].

Mosquito larvicidal:

Aedes aegypti is referred to as yellow fever mosquito, which is a vector for communicating severe tropical fever. This mosquito is responsible for spreading dengue fever, chikungunya, zika virus and other diseases. Thus, control of this mosquito larvae is required which is classically done by organophosphates and insect growth regulators. However, these remedies have limitations including widespread damage to the environment and emergence of resistance. Thus, to combat these problems, now emphasis is being posed over the use of phytoherbal remedies. In this context, *P. longum* extract was examined, reporting 100% mortality against larvae. Further, piperonaline was isolated and identified as the bio-active component of *P. longum* which was responsible for larvicidal action, although piperine, piperlongumine, and piperettine did not show any action against the larva [14].

Acaricidal:

Rhipicephalus (Boophilus) microplus and *Hyalomma anatolicum* are the two ticks species which are responsible for spreading disease to cattle and humans. These ticks are distributed to hot and dry regions of India and are causing a lot of economic loss to dairy industry. The prevention of these ticks are done by so called acaricides and vaccination, but the growth of resistance are making demand for newer agents. Aqueous and ethanol extract of *P. longum* showed acaricidal activity against three-host ixodid tick, *Hyalomma anatolicum* [14].

Reproductive system:

The evidence of *P. longum* to demonstrate contraceptive properties came from the fact that it's one of the Ayurvedic formulation referred as Pippalyadi vati, and its individual constituents are used as a contraceptive for women since ancient times . Thus, studies have been performed to validate the action of *P. longum* for infertility action. It has been claimed that *P. longum* interferes with the regular progression of reproductive senescence and encourages infertility through gonadotropin inadequacy and variation of inflammatory intermediaries . Moreover, *P. longum* was also employed for spermicidal activity against human spermatozoa [14].

Anti-snake venom:

Snake bites in tropical developing countries lead to serious clinical manifestations including hemorrhage, shock, acute kidney, and local tissue damage. Anti-venom therapy is mainly given through intravenous route, which is expensive and delay in their availability at the site of accident leads to fatality. Thus, other measures are being considered which delays the onset of toxicity. Herbal medicines are gaining interest worldwide and help in revealing the symptoms of snakebite such as pain, anxiety, reducing local effects, produce anti-inflammatory action, thus preventing lethality . Fruit extract from *P. longum* was evaluated against snake venom in embryonated fertile chicken eggs, mice and rat. Inhibition of venom lethal action, hemorrhagic action, necrotizing action, defibrinogenating action, paw edema, mast cell degranulation, creatine kinase assay and catalase activity were examined and were brought to normal level at the doses of 250 mg/kg, 500 mg/kg and 750 mg/kg. This study provides evidence that plant extract can be used to reduce lethality and can be considered in rural areas where folk medications are accessible [14].

Bio-enhancer:

The rate and extent of reaching a drug into systematic circulation is referred to as bioavailability. The drugs given by intravenous route demonstrate maximum bioavailability, though when drugs are given via oral route the extent to cross the cellular barrier decreases. Thus, decrease in bioavailability increase the dose required to produce action. Bioenhancers are the agents that increase the bioavailability and bio-efficiency of particular drug. The addition of trikatu or one its ingredient in wide range of ayurvedic formulation is due to their bioenhancer activity. Moreover, various mechanisms have also been put forward to analyze the bio-enhancer action of piperine, which comprises of DNA receptor binding, modulation of cell signal transduction and inhibition of drug efflux pump, inhibiting enzymes participating in biotransformation of drugs [14].

Ginger (*Zingiber officinale*)

Ginger has been used for thousands of years for the treatment of numerous ailments, such as colds, nausea, arthritis, migraines, and hypertension. The medicinal, chemical, and pharmacological properties of ginger have been extensively reviewed [15].

Bioactive components of ginger

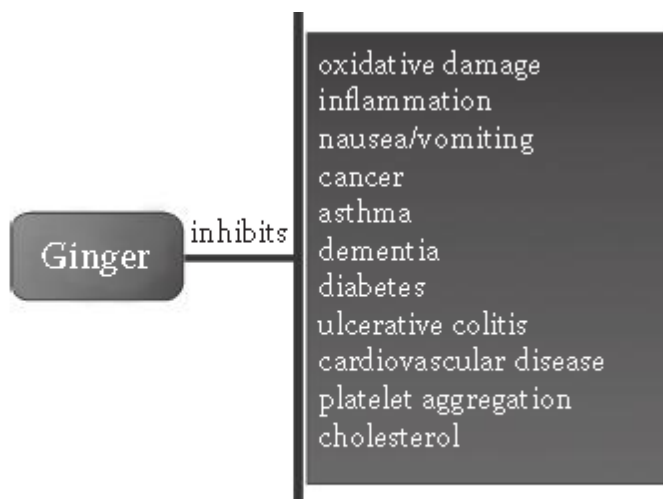
At least 115 constituents in fresh and dried ginger varieties have been identified. Gingerols are the major constituents of fresh ginger and are found slightly reduced in dry ginger, whereas the concentrations of shogaols, which are the major gingerol dehydration products, are more abundant in dry ginger than in fresh ginger. At least 31 gingerol-related compounds have been identified from the fresh ginger rhizome. Ginger has been fractionated into at least 14 bioactive compounds, including such as [4]-gingerol, [6]-gingerol, [8]-gingerol, [10]-gingerol, [6]-paradol, [14]-shogaol, [6]-shogaol, 1-dehydro-[10]-gingerdione, [10]-gingerdione, hexahydrocurcumin, tetrahydrocurcumin, gingerenone A etc [15].

HEALTH EFFECTS: THE SCIENTIFIC EVIDENCE

General Antioxidant Properties of Ginger

Anti-Inflammatory Effects of Ginger

Patients suffering from osteoarthritis of the knee showed a consistently greater response to treatment with ginger extract compared with the control group. In addition, relief from pain and swelling was reported in patients suffering from rheumatoid arthritis, osteoarthritis, or general



The variety of protective effects wielded by ginger.

muscular discomfort when using powdered ginger as a dietary supplement for 3 months to 2 years. Besides pain relief from arthritis, results of a double-blind comparative clinical trial indicated that ginger (250-mg capsules) was as effective as the nonsteroidal anti-inflammatory drugs mefenamic acid (250 mg) and ibuprofen (400 mg) in relieving pain in women with primary dysmenorrhea. The anti-inflammatory effects of ginger might be related to its ability to inhibit prostaglandin and leukotriene biosynthesis. Some others have showed that gingerols actively inhibit arachidonate 5-lipoxygenase, an enzyme of leukotriene biosynthesis. Others have also reported that ginger extract suppresses the activation of tumor necrosis factor α (TNF- α) and expression of COX-2 in human synoviocytes [15].

[6]-gingerol was reported to inhibit the production of proinflammatory cytokines such as TNF- α , interleukin (IL)-1 β , and IL-12 from LPS-stimulated peritoneal macrophages [15].

In general, ginger extract inhibited macrophage activation and APC function, and indirectly suppressed T-cell activation. Some of ginger's anti-inflammatory effects appear to be associated with decreased I κ B α degradation and impaired nuclear factor κ B (NF- κ B) nuclear translocation of p65 [15].

Ginger as an Antinausea Agent:

The most common and well-established use of ginger throughout history is probably its utilization in alleviating symptoms of nausea and vomiting. The benefits and dangers of herbal treatment of liver and gastrointestinal distress have been reviewed and several controlled studies have reported that ginger is generally effective as an antiemetic. The effectiveness of ginger as an antiemetic has been attributed to its carminative effect, which helps to break up and expel intestinal gas. Ginger root is commonly recommended for preventing seasickness. Several double-blind, randomized, placebo-controlled clinical trials have indicated that ginger consumption is effective and safe in helping to prevent nausea and vomiting during pregnancy. Ginger has been recommended to combat nausea associated with chemotherapy [15].

Anticarcinogenic Activities of Ginger:

The effectiveness of ginger in preventing or suppressing cancer growth has been examined in a variety of cancer types, including lymphoma, hepatoma, colorectal cancer, breast cancer, skin cancer, liver cancer, and bladder cancer. The mechanisms proposed to explain the anticancer activities of ginger and its components include antioxidant activity and the ability to induce apoptosis, decrease proliferation, cause cell-cycle arrest, and suppress activator protein 1 (AP-1) and NF- κ B/COX-2 signaling pathways. Studies suggest that ginger compounds suppress proliferation of human cancer cells through the induction of apoptosis [15].

Ginger extract and especially [6]-gingerol were reported to effectively decrease proliferation of YTT colon cancer cells. [6]-shogaol, an alkanone from ginger, exhibited the most potent cytotoxicity against human tumor cells. [6]-shogaol induced apoptosis of hepatoma cells mediated by activation of caspase-3 and -7. The compound was also reported to reduce the viability of gastric cancer cells by directly damaging microtubules and inducing mitotic arrest. [6]-gingerol might exert its effects by suppressing the NF- κ B/COX-2 pathway [15].

Cardiovascular and Other Disease-Preventive Effects of Ginger:

Ginger has gained interest for its potential to treat various aspects of cardiovascular disease, and the in vitro and animal data supporting the anti-inflammatory, antioxidant, antiplatelet, hypotensive, and hypolipidemic effects of this condiment have been reviewed. ginger has no effect on blood pressure, heart rate, or coagulation parameters and does not interact with

anticoagulant drugs such as warfarin. An aqueous ginger extract was reported to induce a dose-dependent decrease in arterial blood pressure in a variety of animal models [15].

Importantly, ginger powder (3 g/day in 1-g capsule 3xd) significantly lowered lipid levels in volunteer patients in a double-blind, controlled clinical trial study. Triglyceride and cholesterol were substantially decreased as was LDL levels compared to placebo group [15].

Antiplatelet therapy is an effective approach for preventing coronary heart disease. Ginger components are suggested as a potential new class of platelet-activation inhibitors without the potential side effects of aspirin, which is most commonly used in this approach [15].

Asthma:

Asthma is a chronic disease characterized by inflammation and hypersensitivity of airway smooth muscle cells to different substances that induce spasms, and ginger has been used for centuries in treating respiratory illnesses. Components of ginger rhizomes are reported to contain potent compounds capable of suppressing allergic reactions and might be useful for the treatment and prevention of allergic diseases. It was reported that a ginger extract inhibits airway contraction and associated calcium signaling, possibly by blocking plasma membrane calcium channels. Dried ginger may have beneficial effects in treating dementia, including Alzheimer's disease [15].

Piper nigrum L.

Piper nigrum L., most commonly known as pepper, is considered to be the “king of spices” because of its massive trade share in the global market. The name “pepper” originates from the Sanskrit word pippali, which means berry [16].

Pharmacological properties of *P. nigrum*:

P. nigrum and its bioactive compounds were also found to possess other important pharmacological properties including antimicrobial, antioxidant, anticancer, analgesic, anticonvulsant, neuroprotective, hypoglycemic, hypolipidemic, and anti-inflammatory activities [16].

Habitat and Cultivation of Piper Plants:

Piper nigrum is a member of the family Piperaceae and is originally native to India. The plant is well known for its medicinal properties. It is the most commonly used spice, thus also called “the King of Spices”. Different types of black peppers are available having different colors. Black pepper has a wide range of applications. It is used as medicine, as a preservative and is also used in perfumes. The active components of *P. nigrum* are used in foods as well as medicine. Pepper is used in sauces and meat dishes throughout the world. It contains an alkaloid called piperine which is known for its remarkable pharmacological actions, including antioxidant, antihypertensive and antiplatelet, antiasthmatics, analgesic, antitumor, antipyretic, antispasmodic, antidepressant, antidiarrheal, anxiolytic, anti-inflammatory, immunomodulatory,

hepatoprotective, antifungal, antibacterial, antimutagenic, larvicidal, insecticidal, and many other activities. Piperine inhibits several metabolic enzymes and increases the oral bioavailability of many vaccines, drugs, and nutrients ultimately enhancing their therapeutic effects. Piperine also helps in digestion by stimulating the intestinal and pancreatic enzymes. Piperine is the only main constituent responsible for most of the therapeutic actions of this spice. The fruits of *P. nigrum* are utilized to produce green and white peppers. The fruit of *P. nigrum*, also known as peppercorn, in mature form seems dark red while in the dried form it appears as a small black wrinkled drupe with a diameter of 5 mm [16].

Chemical Composition:

Around 135 compounds in these EOs were recognized, belonging to the monoterpene, sesquiterpene, aliphatic, aromatic and other chemical groups. Generally speaking the EOs are composed by 70–80% of monoterpene hydrocarbons (mainly α -pinene up to 13%, β -pinene up to 40%, limonene up to 32%), 20–30% sesquiterpene hydrocarbons (mainly β -caryophyllene up to 22%) and less than 4% oxygenated constituents [16].

The root of *P. nigrum* is used by the people of Thailand in the form of ghee, powders, enemas, and balms to treat abdominal tumors, abdominal fullness, adenitis, cancer, cholera, cold, colic, kidney stone, asthma and headache. In addition, the plant is also used in traditional Chinese medicine to treat epilepsy and applied in some formulae to treat respiratory or gastric cancers in China. *P. nigrum* is also used in traditional Middle Eastern medicine as a nerve tonic. In traditional Ayurvedic medicine, *P. nigrum* is used in combination with *P. longum* to treat intermittent fevers, to promote the secretion of bile and recommended for neurological, broncho-pulmonary and gastrointestinal disorders, (including dyspepsia, flatulence, constipation and hemorrhoids). The folk medicine uses of fruits and leaves of *P. nigrum* for the treatment of coughs, intestinal diseases, bronchitis, venereal diseases, and rheumatism were reported, while the general application of *P. nigrum* for treating diarrhea, fever, cold, colic disorder and gastric conditions were cited. The usages of *P. nigrum* as a stimulating expectorant in traditional Western and Ayurvedic medicines, and as a tranquilizing and anti-emetic in traditional Chinese medicine was also reported. Moreover, the seed is applied internally in Western herbalism to treat indigestion and wind, and in Chinese medicine to treat stomach chills, food poisoning, cholera, dysentery, diarrhoea and vomiting caused by cold. Furthermore, *P. nigrum* is used externally in Ayurvedic medicine to treat nasal congestion, sinusitis, epilepsy and skin inflammations with the EO used to ease rheumatic pain and toothache. Particularly, *P. nigrum* (black pepper) is the most important species of this genus due to its pungent principle component, piperine, and its worldwide popularity as a flavoring for food [16].

Antioxidative Activity:

The black pepper EO showed strong antioxidant activity in comparison with synthetic oxidants. The results of this study demonstrated that black pepper can be used as an easily accessible source of natural antioxidants and as a safe food preservative [16].

Antimicrobial Activity:

Black pepper (*P. nigrum*) volatile oil has been proven to have antimicrobial activity. The phenolic compounds of black pepper are believed to be responsible for this antimicrobial activity

by damaging the membranes of bacteria restricting their growth . Black pepper has also been shown to exhibit antibacterial activity with reported minimum inhibitory concentrations (MICs) of around 50–500 ppm and inhibition of Gram-positive bacteria such as *Staphylococcus aureus*, followed by *Bacillus cereus* and *Streptococcus faecalis*. In addition, black pepper has demonstrated inhibition against some Gram-negative bacteria such as *Pseudomonas aeruginosa*. Black pepper EO is composed primarily of monoterpenes and sesquiterpenes. This EO has also been used to inhibit the growth of microorganisms such as *Vibrio cholerae*, *Staphylococcus albus*, *Clostridium diphtheriae*, *Shigella dysenteriae*, *Streptomyces faecalis*, *Bacillus spp.* and *Pseudomonas spp.* in addition to suspending the growth and production of aflatoxins produced by *Aspergillus parasiticus*. These effects are due to chemical constituents such as piperazine, piperanine, piperidine A and piperolein B [16].

Antiparasitic Activities of Piper Species:

Numerous Piper species are used in traditional medicine to treat parasitic diseases.

Among protozoa, the main parasites targeted were *Plasmodium falciparum*, *Trypanosoma cruzi* and *Leishmania spp.*, causal agents of malaria, Chagas disease and leishmaniasis, respectively, and represent the more important protozoal diseases with respect to the mobility and mortality caused by these agents [16].

P. nigrum (black pepper) is among the most extensively studied species for its neuropharmacological activities. Anxiolytic, antidepressant, neuroprotective and anti neuro-inflammatory effects of *P. nigrum* extracts have been examined in multiple animal studies [16].

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