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RESEARCH ARTICLE

PRECIOUS PHYTOMEDICINAL COMPONENTS OF TULSI (*Ocimum Sanctum* Linn.) AND THEIR THERAPEUTIC IMPORTANCE

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ABSTRACT

Tulsi (holy basil), "Queen of herbs" is the blessing of our nature. There are different types of tulsi plants. Among them, *the Ocimum sanctum* is very popular in the culture of the Hindu religion and the perspective of ethnomedicine. The medicinal uses of tulsi were started in ancient times. Its medicinal values were described in the Indian classical herbal medicinal book "Charaka Samhita". The modern civilized society still uses this valuable plant as alternative and complementary medicine. The aqueous or alcoholic extract of *Ocimum sanctum* contains flavonoids, alkaloids, polyphenolic compounds, eugenol, ursolic acid, carvacrol, linalool, etc**.** Different parts (leaves, seeds, stem), or extract (herbal tea, juice) of tulsi are used for medicinal purposes. The biopotential compounds of tulsi are active for the prevention and cure of many illnesses like cough, bronchitis, asthma, common cold, fever, hepatic diseases, skin diseases, arthritis, and digestive disorders. Applications of tulsi as herbal medicine improve the various pathological conditions without any major complications or side effects. The present paper is related to the botanical description of the Tulsi plant, its bioactive components, their pharmacological activities.

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INTRODUCTION

Natural medicinal plants are the most valuable blessings of nature for human beings. In this millennium, peoples are searching for traditional medicine for the cure of several diseases by avoiding the toxicity and ill-effects of chemical drugs. For this purpose, nature has provided a complete storehouse of medicinal plants for mankind. According to the World Health Organization (WHO), a medicinal plant is any plant where substances that can be used for therapy reside in one or more of its organs (Mousavi *et al*., 2018). Tulsi (Tulasi in Sanskrit, holy basil in English) is a wonderful medicinal aromatic herb. It is commonly treated as a holy plant, used for the worship of Lord Vishnu in Hinduism. Different species of tulsi plants are present in the various parts of South-East Asia (Indian subcontinent) (Juyal and Ghildiyal, 2017). All these plants are aromatic perennial plants; they belong to the genus *Ocimum* under the family Lamiaceae (Table 1). The name 'Tulsi' was originated from the name of Tulasi Devi, an eternal partner of Lord Krishna. In most cases, Indian citizens nurture the tulsi plants for their spiritual purposes.

The leaves of tulsi are used in houses and temples for worship. However, tulsi cultivation was popular from ancient times for its traditional ethnomedicinal value. The study of chloroplast genome sequences indicated that the plant was originated from North Central India (Watson and Preedy, 2011; Naquvi *et al*., 2012; Bast *et al*., 2014). Thus the plant is indigenous to the Indian subcontinent. The use of this plant was started in ayurvedic medicine more than 3000 years ago. The application of tulsi was found in the Rig-Veda (3500-1600 BC). According to Ayurveda tulsi is often treated as an "Elixir of Life" for its potential activities against rhinitis, common cold, bronchitis, asthma, hiccups, skin and hematological diseases, parasitic infections, rheumatism, wound healing, cardiovascular disease, gastric disorders, insect biting, epilepsy, malaria, and inflammation (Puri, 2002; Sharma *et al*., 2013a; Vidhani *et al*., 2016). The leaves extract has been given for the treatment of respiratory problems, while the tea infusion can be applied for the treatment of stomach and liver diseases. *Ocimum sanctum* (Linn.) can be used in different forms, including herbal tea, dry powder, or natural leaves.

The extract of tulsi acts as an anti-inflammatory, antioxidant, immunomodulatory, anti-carcinogenic, and stress-reducing agent (Siva *et al*., 2016). The present review has focused on phytochemical compounds and their pharmacological importance.

OUTLINE MORPHOLOGY OF THE PLANTS: Tulsi is a common tropical plant, grown in the moist soil of warm regions. The plant Tulsi is an erect, branching herb or under-shrub, aromatic, 30–60 cm tall covered with minute fine hairs (Singh, 2015; Bano *et al*., 2017). Leaves are green or purple, up to 5 cm long blade; these leaves are simple, petioled, elliptic, oblong, and obtuse having a little toothed margin; they have strong fragrant and a decussate phyllotaxy (Kumar *et al*., 2013). The purplish/reddish flowers are placed in close whorls on elongate racemes (Fig.1) (Sharma *et al*., 2013a). The flowers are arranged in short cylindrical spikes with rigid clusters (Kumar *et al*., 2013). The base of flowers bears stalkless heart-shaped bracts. Generally, the flower is 5 mm in length, the calyx tube is bearded outside the base, and the flower tube is hairy (Singh, 2015). The fruits are tiny. Seeds are yellowish to reddish. The normal taste of the plant is acrid and bitter. The common morphological variations of different types of tulsi (different species of *Ocimum)* are given in Table 1.

CHEMICAL CONSTITUENTS: Medicinal plants are commonly rich sources of secondary metabolites and essential oils. The most important biopotential phytochemicals are phenolics, flavonoids, alkaloids, essential oils, saponin, and tannins s (Krishnaiah *et al*., 2009). The chemical composition of the extract of *Ocimum sanctum* L. is highly complex, containing essential oils, flavonoids, alkaloids, polyphenolic compounds, saponins, tannins, anthocyanins, triterpenoids, eugenol, ursolic acid, carvacrol, linalool, limatrol, methyl eugenol, sesquiterpene, caryophyllene, and estragole (Pattanayak *et al*., 2010). Different vitamins (ascorbic acid, vitamin A), minerals (iron, calcium, and zinc), and other phytonutrients are also present in the extract of *Ocimum sanctum* (Anbarasu *et al*., 2007).

The various parts of the *O. sanctum* contain diverse phytochemicals components. The leaves of *O. sanctum* are the greatest source of essential oils. The constituents of this oil are benzene, dimethylbenzene, toluene, octane, camphene, citronellol, sabinene, limonene, ethyl-2-methyl butyrate, ledol, eugenol, iso-eugenol, terpinolene, β-elemene, isocaryophyllene, α-terpeneol, α-amorphene, α-guaiene, α-humulene, borneol, calamine, nerolidol, carvacrol, geraneol, humulene oxide, elemol, tetradecanal, (EZ)-famesol, cissesquisainenehydrate, α-bisbolol, selin-11-en-4-α-ol,α-murolene, 14-hydroxy-α-humulene (Singh *et al*., 2012). The alcoholic extract of leaves and aerial parts of the plant contain luteolin, orientin, ursolic acid, apigenin-7-Oglucuronide, luteolin-7-O-glucuronide, isorientin, aesculin, triacontanolferulate, vallinin acid, gallic acid, circineol, aesculetin, triacontanolferulate, chlogenic acid, stigmasterol, caffiec acid, ursolic acid, 4-hydroxybenzoic acid, vicenin2, chlorogenic acid, procatechuic acid, and phenylpropaneglucosides. The seeds of the plant are also very rich sources of different components. The fixed oils such as oleic acid, stearic acid, hexourenic acid, palmitic acid, linodilinolin, and linolenic acid are present in seed constituents. Fresh leaves and stems are the rich sources of phenolic compounds like apigenin, circimaritin, isothymusin, eugenol and rosameric acid (Bhowmik *et al*., 2008). Basak *et al*. (2013) reported that the extract of *O. sanctum* also contain monoterpenes and sesquiterpenes (neral, campene, phytosterol, and stigmasterol). The various bioactive components, their chemical characteristics, and therapeutic importance are given in Table 2.

PHARMACOLOGICAL USES: The pharmacological actions of tulsi were fully described in the Charaka Samhita. The leaves of tulsi (dried or fresh) are commonly used. Despite leaves, stem, seeds, and sometimes whole plants are also the usable part. All the parts of the *O. sanctum* are fully rich with biopharmaceutical compounds. From ancient times, it was used for the treatment of rhinitis, cough, headaches, gastric problems, various forms of poisoning, and others (Gupta *et al*., 2002). Numerous studies indicated that the bioactive compounds of tulsi have potent pharmacological benefits against microbial infection, metabolic disorders like diabetes, inflammatory response, cancer progression, oxidative stress, and hepatic dysfunction (Fig. 2) (Gupta *et al*., 2002; Satyavati *et al*., 2008).

Antimicrobial activity: Tulsi exhibit antimicrobial activity against various bacteria and fungi like *Staphylococcus aureus*, *Escherichia coli, Shigella sp., Enterobacteria* sp., *Pseudomonas aeruginosa, Salmonella typhimurium, Shigella dysentriae*, *Vibrio* sp., *Klebsiella pneumonia, Proteus mirabilis, Bacillus anthracis*, *Bacillus subtilis*, *Mycobacterium tuberculosis, Micrococcus pyogenes*, and *Candida albicans* (Vidhani *et al*., 2016; Kumar *et al*., 2013; Rahman *et al*., 2010; Mishra and Mishra, 2011; Wang *et al*., 2013). The essential oil of *O. sanctum* contains caryophyllene; eugenol, methyl eugenol, which are responsible for their antibacterial activity. These components are effective against *E. coli*, *B. subtilis*, *B. anthracis*, *S. aureus, Pseudomonas vulgaris,* and *P. aeruginosa* (Bano *et al*., 2017). Singh *et al*. (2005) indicated that a higher amount of linoleate in tulsi extract has anti-bacterial activity. Similarly, Geeta *et al.* (2001) reported that aqueous extract of *O. sanctum* L. (60 mg/kg) exhibits inhibitory effects against *Klebsiella*. Ursolic acid, eugenol, and carvacrol are the known bioactive components. They are commonly present in aqueous, ethanolic, methanolic extract. These compounds show antimicrobial activity (Agarwal *et al*., 2010). The aqueous extract of *O. sanctum* gives better results against beta-lactam antibiotics resistant microbe such as *S. aureus* and drug-resistant strains of *Neisseria gonorrhea.* The oils of tulsi are active against acne-forming bacteria *Propioni bacterium* (Bano *et al*., 2017).

The extract of *O. sanctum* fights against filamentous fungi like *Aspergillus Niger, A. fumigatus*, *A. flavus, Rhizopus stolonifera Penicillium digitatum Candida albicans*, *Cryptococcus neoformans*, *Microsporum cassis*, *Sporotrichum schenkii* as well as *various* pathogenic fungi, including *Alternaria solani*, *Candida guillermondii*, *Colletotricum capsici*, *Curvularia* spp., *Fusarium solani*, *Helminthosporium oryzae, P. funiculosum, Rhizomucor tauricus*, and *Trichoderma reesi* (Bano *et al*., 2017; Bansavatar *et al*., 2015). The efficacy of the tulsi extract was also tested on clinically isolated most common dermatophytic fungi such as Microsporum, epidermophyton, and trichophyton. The minimum fungicidal concentration (MFC) was 200µg/mL. It is assumed that secondary metabolites like alkaloids, glycosides, saponins, tannins, and eugenol can exert antifungal activity (Balakumar *et al*., 2011). Two components eugenol and particularly linalool show antifungal effects against *Candida* species.

Table1. Systemic position of the plant tulsi along with general characteristics and uses of different species of tulsi

Plant profile
Kingdom: Plantae
Subkingdom: Tracheobionta (Vascular plants)
Superdivision: Spermatophyta (Seed plants)
Division: Magnoliophyta (Flowering plants)
Class: Magnoliopsida (Dicotyledons)
Subclass : Asteridae
Order: Lamiales
Family: Lamiaceae / Labiatae (Mint family)
Genus: *Ocimum*
Species: *sanctum, tenuiflorum*, *gratissimum, basilicum*, *canum, kilimandscharicum*

Scientific Name	Local name or common name	Types of plant	General description of plant	Flowering and fruiting time	Common uses
Ocimum sanctum Linn.	Radha/Sri tulsi	Low shrub	Much-branched, stem sub-quadrangular, covered with soft spreading hairs. Leaves green, elliptic-oblong, obtuse or acute, pubescent on both sides, base obtuse or acute. Flowers in racemes, in close whorls, bracts broadly ovate, pubescent. Corolla purplish. Nutlets broadly ellipsoid, nearly smooth yellow with black margins.	Throughout the year	Roots: use to treat bites of worms and leeches.. Leaves: used for the treatment of cold and common cough, skin diseases, gastric disorders, liver diseases, constipation, ring worm infection, insect bite. Seeds: useful in cases urogenital problems
Ocimum tenuiflorum Linn.	Krishna or Shyama tulsi	Perennial under shrub	Stem striate, covered with soft spreading hairs. Leaves purplish, elliptic-oblong, pubescent. Flowers purplish white in long vericillaster of close whorls. Calyx hairy at the base, long. Nutlets 4, broadly ellipsoid.	Throughout the year	Roots: use to treat malarial fever Leaves: used for the treatment of cold and common cough, asthma, bronchitis, skin diseases, gastric disorders, liver diseases, hematological problems, diuresis, ring worm infection. Seeds: useful in cases urogenital problems
Ocimum gratissimum Linn.	Rama tulsi or Vana tulsi	Low shrub	Much branched, stem erect Leaves dark green, fragrant elliptic or lanceolate. Flowers small, elongated, verticillaster cymes, moderately closed whorls. Calyx gland dotted, puberulous. Corolla pale greenish, yellow Stamens 4. Nutlets 4, brown, subglobose, rugose.	September to January	Whole plant: use to treat skin diseases, liver disorders, seminal weakness, rheumatism, headache. Leaves: useful against asthma, and septic wounds.
Ocimum basilicum Linn.	Misti tulsi / Babui tulsi / Dulal tulsi	Herb	Erect branching. Leaves long, ovate, acute, toothed, base cuneate Whorls densely recemose, the terminal racemes longer than the lateral ones; bracts stalked. Calyx 2-lipped. Corolla white pink or purplish, glabrous or various pubescent. Stamens 4. Nutlets ellipsoid, black and pitted	August to January	Roots: use to treat bowel. Leaves: used for the treatment of ringworm, scorpion sting,. Seeds: useful in cases of gonorrhoea, diarrhea, chronic dysentery, sinuses, and internal piles
Ocimum canum Sims.	Kshudra tulsi / Naya tulsi / ban tulsi	Low shrub	Multi branched. Leaves elliptic-lanceolate, acute on both ends, glabrous. Flowers close whorls in spiciform racemes bracts elliptic-lanceolate, stalk ciliate with white hair. Calyx 2-lipped. Corolla white 2lipped. Stamens 4. Nutlets long ellipsoid, black.	August to December	Leaves: Leaves-paste used for the treatment of parasitical diseases of the skin. Leaves and seeds: anti-rheumatismal and anti-dysenteric.
Ocimum kilimandscharicum Guerke.	Karpur tulsi	Perennial under shrub	Much-branched. Leaves ovate to broadly elliptic, acute, dentate, pubescent on both surfaces, prominently veined. Flowers pale-purple or pinkish-white, brone in 4-6 flowered whorls on long villose racemes at the endof branches. Nutlets ovoid, oblong, bkack to brown in color	August to January	Leaves: used for the treatment of common cold and cough, bronchitis, halitosis, bacterial and viral infections, foul ulcers, wound healing anorexia.

Source: Medicinal plant resources of South West Bengal. 2005. Ed. N. D. Paria; Pub. Directorate of forest, Govt. of West Bengal.

Figure 1. Close view of tulsi (*Oscimum sanctum* Linn.) plant leaves and flower

This effect is helpful to prevent oral candidiasis (Khan *et al*., 2010). Prakash and Gupta (2005) reported that eugenol has anti-viral activity. The study indicated that *Ocimum sanctum* active against Hematopoietic Necrosis Virus (IHNV), herpes virus (HSV), hepatitis B virus, and New Castle Disease Virus (Bano *et al*., 2017; Kumar *et al*., 2013; Direkbusarakom *et al*., 1996; Jayati *et al*. 2013). Bioactive compounds like linalool, apigenin, and ursolic acid have antiviral properties and restrict the growth of DNA viruses and RNA viruses (Kumar *et al*., 2013; Sangeetha and Poornamathy, 2015; Sood *et al*., 2013).

Anti-inflammatory and immune-modulatory activity: Immune defense makes a great challenge against infectious agents. Immune activity depends on the humoral and cell-mediated activity. An inflammatory response is the non-specific immune response against various antigens. Several cytokines and other humoral factors regulate the inflammatory response. Over-stimulation of this response starts hypersensitivity reactions. The inflammatory response is exaggerated by histamine and other anti-anaphylactic mediators. Extract from *Ocimum sanctum* stabilizes mast cell and inhibits IgE mediated degranulation to stop the release of histamine and other inflammatory mediators (Siva *et al*., 2016). Ursolic acid of tulsi leaf prevents nuclear factor (NF)-κB mediated gene expression. The NF-κB plays a crucial role in the inflammatory activity, which modulates the expression of several genes of inflammatory cytokines. NF-κB has five subunits [NFκB1 (p50), NFκB2 (p52), RelA (p65), RelB, and cRel]. The active form of NF-κB is a homodimeric or heterodimeric complex. The RelA and p50 give a heterodimer that triggers the expression of pro-inflammatory cytokine, adhesion molecules, and enzymes [inducible nitric oxide (iNOS); cyclooxygenase 2 (COX-2)]. Before initiation of inflammation, the function of NF-κB is inhibited by an inhibitory protein, known as inhibitory κ-B (IκB). At the time of inflammation, IκB kinase (IKK) is activated, which phosphorylates IκB for its dissociation from NF-κB and helps the nuclear translocation of NF-κB. NF-κB starts the transcription of genes related to the inflammatory response. Ursolic acid prevents the degradation and phosphorylation of IκB, IKK activation, p65 phosphorylation, p65 nuclear translocation as well as, and NF-κB dependent reporter gene expression. The methanolic extract and aqueous suspension of *O. sanctum* exhibit the proprieties of anti-inflammatory effects in rats. The fixed oil and linolenic acid block the activity of lipoxygenase and cyclooxygenase pathways to prevent the synthesis of inflammation modulatory agents, prostaglandin, and leukotriene (Singh and Majumdar, 1997). The anti-inflammatory action of oils from fresh leaves and seeds of *O. sanctum* was also tested on carrageenan-induced paw edema and croton oil-induced granuloma formation. Both these appearances are the common symptom of inflammatory response. The experimental result showed that the administration of essential oil of *O. sanctum* gave promising results against inflammatory response, but the potentiality was low compared to the standard drug, flurbiprofen (Singh and Agrawal, 1991). Singh (1998) reported that fixed oil of tulsi can prevent the extravasation of leukocytes during the inflammatory response. The aqueous extract of *O. sanctum* enhances antibody production cell-mediated cytotoxicity in albino rats (Mukherjee *et al*., 2005). The experimental result of the human trial was reported by Mondal *et al*. (2011). A small randomized double-blind, and placebo-controlled trial was performed.

Application of ethanolic tulsi leaf extract increases natural killer (NK) and T-helper cells in healthy adult participants compared to placebo volunteers.

Anti-diabetic activity: Diabetes mellitus, especially type 2 is a global problem. There are several treatments to control the hyperglycemic condition, but the sensitivity of the drug decreases after a certain time. Herbal medicine may be the alternative treatment for several metabolic disorders including type 2 diabetes. Oral administration of *O. sanctum* extract has the ability to reduce blood sugar in the experimentally prepared diabetic rats (Siva *et al*., 2016). Application of eaves extract of *O. sanctum* in streptozotocin-treated diabetic rats improves the action of glucokinase, hexokinase, and phosphofructokinase as well as tissue glycogen content (Vats *et al*., 2004). The randomized clinical trials with placebo controls showed that administration of *O. sanctum* extract reduces fasting and postprandial glucose levels compared to controls. Supplementation of tulsi extract with hypoglycemic medicine significantly improves HbAic levels in comparison with hypoglycemic drug treatment alone (Somasundaram *et al*., 2012). Another study also reported that tulsi extract affects the symptoms of type 2 diabetes-like polydipsia, polyphagia, polyuria, sweating, fatigue, burning feet, itching, and headache (Sharma and Sachdeva, 2009). Mandal *et al*. (1993) indicated that components of *O. sanctum* leaf extracts exert an inductive effect on insulin secretion. The leaf extracts contain several types of antioxidants for free radical scavenging. This effect protects pancreatic islets against stress and promotes insulin secretion.

Anticancer effect: The progression of cancer is a serious problem in our modern society. In recent years, cancer is one of the leading causes of death throughout the world. Chemotherapy is a common treatment for cancer having severe side effects. In this context, potential herbal medicine may be an alternative for this treatment purpose. Tulsi extract shows excellent anti-cancer properties. Although, there is no definite cause of cancer; several factors (environmental pollutants, food additives, and some viral infections, and metabolic disorders, chemical, and physical carcinogens) are responsible for the development of cancer. Viral infections sometimes activate proto-oncogene to an oncogene. Carcinogens are activated through biotransformation reactions within the body. Carcinogens and metabolic disorders increase oxidative stress and disturb redox homeostasis. Normally, the detoxification of carcinogens and mutagens within the body is mediated by several detoxifying enzymes such as glutathione-S-transferase, cytochrome P450, and aryl hydrocarbon hydroxylase. The alcoholic extract of *O. sanctum* leaves influences the activity of

these detoxifying enzymes (Banerjee *et al*., 1996; Manikandan *et al*., 2007). The anti-carcinogenic properties of tulsi leaves' extract had been tested in different carcinoma. The effect of paste, aqueous, and alcoholic extract of leaves of *O. sanctum* were tested on 7,12-dimethylbenz(a) anthracene (DMBA)-induced hamster buccal pouch carcinogenesis. The topical use of paste exhibited promising effects. The microscopic and electrophoretic studies showed the shrinkage of cancerous cells and DNA fragmentation respectively. Both aqueous and alcoholic extract of tulsi leaves showed potential anticancer effects against DMBA-induced papillomas and squamous cell carcinoma when given orally. Moreover, the effect of the aqueous extract is better than alcoholic extract (Karthikeyan *et al*., 1999a). Karthikeyan *et al*. (1999b) had studied the effect of tulsi extract in both *in vitro* and *in vivo* systems. The ethanolic extract of *O. sanctum* leaves shows the result of DNA fragmentation (both in the microscopic and electrophoretic study) in HFS-1080 cells during *the in vitro* study. The Sarcoma-180 cells were introduced to the hind limb of Swiss albino male mice for *in vivo* study. The ethanolic extract of tulsi significantly decreases the tumor volume and survival rate after the 4th week of the scheduled treatment. Pro-carcinogens are converted to carcinogens through Phase I reactions. Tulsi extract prevents metabolic activation of the pro-carcinogen to a carcinogen (Prashar *et al*., 1998). The experimental result indicated that the administration of tulsi extract before treatment of DMBA blocks the activation of DMBA by inhibiting phase I enzymes. Tulsi extract also reduces lipid and protein oxidation and influences phase II reactions for the excretion of xenobiotic compounds (Prashar *et al*., 1998). The result is protection against carcinogenesis.

The appearance of a hypoxic environment is very common in the tumor mass of cancerous growth. Local hypoxia changes the pathophysiological conditions in the microenvironment of solid tumors. Hypoxia induces the expression of hypoxia-inducible factor-1 (HIF-1α) that induces the transcription of hundreds of genes associated with the survival of cells in hypoxic conditions (Samanta *et al*., 2018). HIF-1α regulates expression of numerous essential genes including IGF2 (insulin-like growth factor 2), TGF-α, β3 (transforming growth factor α, β3), VEGF (vascular endothelial growth factor), NOS (nitric oxide synthase), Kir 14 (keratin 14), Kir18 (keratin 18), vimentin, Epo (erythropoietin), heme oxygenase-1 (HO-1), adenylate kinase, transferrin, ceruloplasmin, hexokinase 1, glucose transporter 1(GLUT1), enolase, glucose-6-phosphate isomerase, phosphofructokinase 1, transglutaminase-2, and leptin for cell proliferation, survival, cytoskeletal reorganization, erythropoiesis, angiogenesis, glucose transport and metabolism (Semenza, 2010; Masson and Ratcliffe, 2014). The extract of tulsi has an impact on some factors inducing cancer. Application of tulsi extract decreases the levels of cytokeratin, VEGF, proliferating cell nuclear antigen (PCNA), glutathione-*S*-transferase, antiapoptotic protein Bcl-2 and simultaneously increases the proapoptotic proteins Bax, cytochrome c (Manikandan *et al*. 2007).

The ethanolic extract of *O. sanctum* contains eugenol, luteolin, ursolic acid, and oleanolic acid in different ratios. Eugenol promotes the production of reactive oxygen species, and increases mitochondrial permeability for the release of cytochrome c, and lowers the levels of anti-apoptotic protein bcl-2. These activities facilitate the apoptosis of tumor cells (Yoo *et al*., 2005; Kim *et al*., 2005). Another component luteolin inhibits cellular proliferation, angiogenesis, and metastasis; alternatively stimulates apoptosis of the transformed cells. Cancer cell alters the activity of several factors and enzymes including NF-κB, phosphatidylinositol 3′-kinase (PI3K)/Akt, and X-linked inhibitor of apoptosis protein (XIAP). Luteolin increases the expression of the p53 gene (Lin *et al*., 2008). Ursolic acid (C_{30}) is the major constituent of the extract of tulsi. It is the derivative of squalene (C_{30}), formed by the action of specific cyclase. Inflammatory response and carcinogenesis are mechanically correlated. Ursolic acid inhibits the activity of two important enzymes inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2), which are related to the inflammatory response. Ursolic acid also suppresses the expression genes of these two enzymes (Sporn and Suh, 2000). Thus, the action of the extract of *O. sanctum* towards antioxidant, anti-inflammatory, anti-angiogenesis, metabolic regulation, cell cycle regulation, and apoptosis can regulate cell proliferation, invasion, angiogenesis, and cell survival; these factors ultimately control the cancer progression.

Cardio-protective activity: Tulsi juice is treated as a cardioprotective agent, prevents the cardiac attack, decreases stress, and shows normotensive effects. Long-term use of *O. sanctum* gives cardioprotective activity against isoproterenol-induced myocardial necrosis in Wistar strain. Fixed oil of *O. sanctum* increases clotting time as similar to aspirin. This activity is mediated by inhibiting the aggregation of platelets. Linolenic acid of *O. sanctum* fixed oil is metabolized to eicosapentaenoic acid (EPA). EPA is then converted to PGI3 and thromboxane A3 (TXA3) through the cyclooxygenase pathway but decreases the production of TXA2. Unlike TXA2, both TXA3 and PGI3 prevent platelet aggregation. Hence, the synergistic effects of PGI3 and TXA3 contribute to the prevention of intravascular coagulation (Singh *et al*., 2001). The antioxidant property of *O. sanctum* protects the cardiac muscle from oxidative damage. The experimental result indicated that oral supplementation of extract of *O. sanctum* in rats enhances endogenous antioxidants levels to protect cardio-myocytes during isoproterenol-induced myocardial necrosis (Sood *et al*., 2010). Oral administration of hydroalcoholic extract of *O. sanctum* in albino rats increases cAMP levels and activities of ROS preventing enzymes superoxide dismutase and catalase in myocardial (Sood *et al*., 2006). Extract of *O. sanctum* restores the action of myocardial SOD, GPx, as well as reduced glutathione content in isoproterenol-induced myocardial damage rats (Sood *et al*., 2005).

Gastro-protective effect: Several experiments established the gastroprotective effect of *O. sanctum.* Application of alcoholic extract of *O. sanctum* leaves exhibited ulcer protective effects against cold-restraint stress (65.07%), pyloric ligation (62.06%), aspirin (63.49%), and alcohol (53.87%) induced gastric ulcer models in rats (Mandal *et al*., 1993; Dharmani *et al*., 2004). The leaves extract of *O. sanctum* contains different types of flavonoids and polyphenolic compounds. These components exert potent antioxidant effects. The formation of gastric ulcers is influenced by oxidative stress factors which increases lipid peroxidation, imbalances redox homeostasis, and decreases gastric defensive factors like mucus secretion. The antioxidant properties of leaves extract prevent these oxidative stress-related damages and increase the lifespan of mucosal cells as well as mucin secretion (Goel *et al*., 2005).

Prevention of oral infections: The orientin, eugenol, ursolic acid, carvacrol, sesquiterpene, and β-caryophyllene of tulsi

extract show an antimicrobial property. The application of tulsi extract or paste decreases microbial infections of the oral cavity. Other components eugenol and methyl eugenol can inhibit cyclooxygenase 2 (COX-2) and the production of prostaglandin; this activity shows the analgesic effect (Singh *et al*., 1996).

Hepatoprotective activity: The liver plays a crucial role in metabolism and detoxification. It is frequently exposed to a variety of xenobiotic compounds, pesticides, anesthetics, and drugs. Most of the time, detoxification of these compounds occurs in the liver. Reactive oxygen species (ROS) produce during oxidative stress (OS), detoxification process, and normal cellular metabolism.

ROS initiates lipid peroxidation (LPO), membrane damage, hepatic cell death, and alters redox homeostasis (Dassarma *et al*., 2018). The alcoholic and aqueous extract of tulsi containss flavonoids and polyphenolic compounds, vitamins those have antioxidant activity and act hepatoprotective agent. These antioxidants decrease ROS-mediated oxidative damage and restore redox homeostasis. The study suggested that alcoholic extract of tulsi is hepatoprotective against paracetamol or carbon tetrachloride, and anti-tuberculosis drug-induced hepatotoxicity in male albino rats (Singh *et al*., 2007). The extract of tulsi contains phenols (eugenol, cirsilineol, isothymucin, apigenin and vosamarinic acid) and flavonoids (orientin and vicenin) which show antioxidant activity.

Wound healing: The *Ocimum sanctum* exhibits wound healing property. The adjunct therapies with *O. sanctum* give the better improvement of burn injuries. The wound healing activity of tulsi extract was tested on the excise, incise, and dead space wound model.

The histological examination was performed by using Van Gieson's and Masson Trichome stain. Ascorbic acid, hexose amine, and L-hydroxyproline tulsi extract have wound healing activity (Singh *et al*., 2007). Another study was made on Wistar albino rats through the excision model of wound repair. Application of cold aqueous extract of *Ocimum sanctum* L. leaves along with tumor necrosis factor-α (TNF-α) exhibited epithelization at the site of the wound (Shetty *et al*. 2008). During any type of injury, oxidative stress increases leading to tissue damage. The antioxidant activity of tulsi extract ameliorates the effects of ROS-mediated oxidative tissue damage and promotes the healing process.

Others: Eugenol, palmitric acid, galic acid, vallinin, and ascorbic acid of tulsi are functionally active against dental caries and plaque, and thus, protect the teeth (Aggarwal *et al*., 2011; Ranjana and Tripathi, 2015). Tulsi tonic is also treated as anti ulcerative agents. Tulsi extract has anabolic properties, increases protein synthesis to enhance muscle mass and strength. The essential oil of *O. sanctum* and eugenol exhibits antihelmintic activity during *in vitro* study (Asha *et al*., 2001; Karumari *et al*., 2014). Ursolic acid shows similar properties with albendazole and has the capability to paralyze and kill worms (Pandey *et al*., 2016). Tulsi extract has prostaglandin inhibitory activity and shows antipyretic activity when tested against typhoid, paratyphoid A/B vaccine-induced pyrexia (Kelm *et al*., 2000; Kumar *et al*., 2015).

MODE OF ACTION AND PHARMACOLOGICAL IMPACTS OF COMMON BIOACTIVE COMPONENTS OF *Ocimum sanctum* Linn. (TULSI)

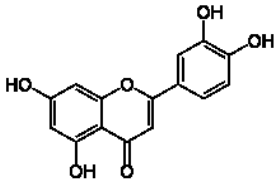
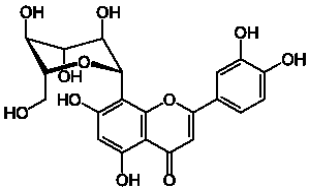
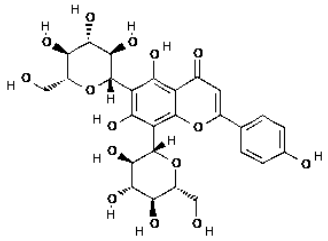
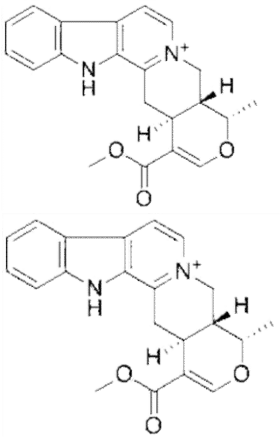
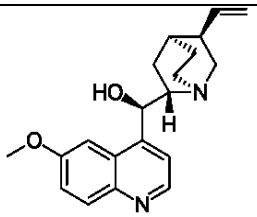
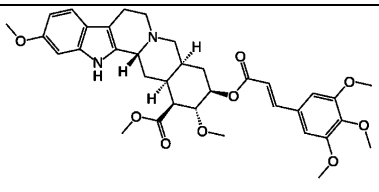
Luteolin: Luteolin a natural flavonoid shows an antioxidant property. It shows several biological effects that are interlinked. Luteolin is a powerful antioxidant, having free radical scavenging property and protects cells from reactive oxygen species (ROS) (Luo *et al*., 2017). ROS-induced damage is being the primary initiator of cancer formation. ROS starts lipid peroxidation resulting formation of lipid peroxide radical. The ROS ($O_2^{\bullet-}$, $^{\bullet}OH$, H_2O_2) and lipid peroxide radicals ($LOO^{\bullet}$) mostly react with dexyguanosine (dG) and deoxy cytosine (dC) of DNA and alters normal characteristics of bases. The antioxidant property protects the cells against oxidative stress (OS). Luteolin inhibits xanthine oxidase activity to stop the formation of $O_2^{\bullet-}$ (Nagao *et al*., 1999).

Luteolin preserves the endogenous redox homeostasis by maintaining the activity of glutathione-S-transferase (GST), glutathione reductase (GR), superoxide dismutase (SOD), and catalase (CAT) (Leung *et al*., 2006; Manju and Nalini, 2005). Luteolin protects the transition metal ions (Fe^{3+}, Cu^{2+}) responsible for ROS generation (Brown and Rice-Evans, 1998). Luteolin shows anti-inflammatory properties and acts as an immune-modulatory agent. It causes inhibition of fatty acid synthase (EC 2.3.1.85). Luteolin inhibits cyclooxygenase (COX) lipoxygenase activity and also suppresses nuclear factor kappa B (NF-κB)-driven inflammatory response (Lin *et al*., 2008). Luteolin exhibits anti-neoplastic activity. It strongly arrests the cell cycle by modulating the expression of CDK, CDK, CDK4, and CDK6 as well as cyclin A, cyclin B, cyclin D, and cyclin E (Massague, 2004). Luteolin inhibits the expression of vascular endothelial growth factor (VEGF) receptor antagonist. The inhibition of VEGF activity prevents angiogenesis. It inactivates HIF-1α by promoting p53-mediated proteasomal degradation (Hasebe *et al*., 2003).

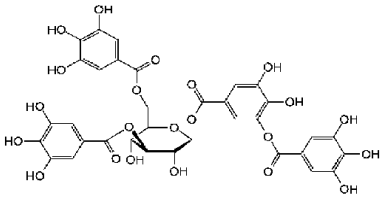
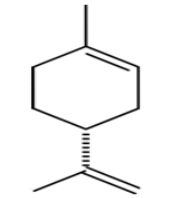
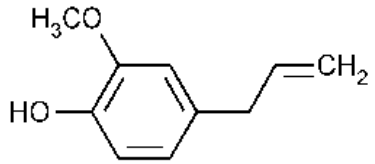
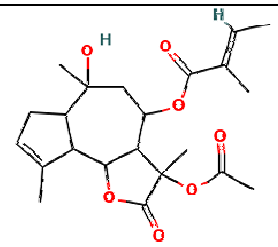
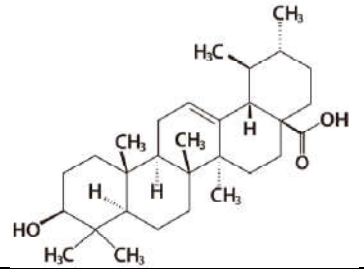
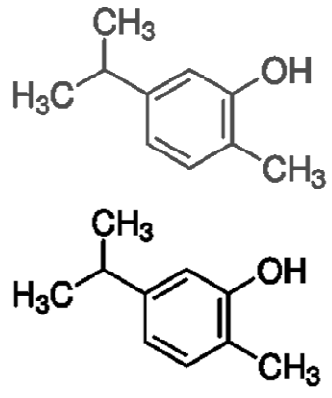
Luteolin suppresses metastasis by inhibiting matrix metalloproteases (MMPs) (Ende and Gebhardt, 2004). A recent report suggested that luteolin blocks the intravasation of MDA-MB231 breast cancer spheroids by inhibiting MMP1 and also modulating the lymph endothelial cell (LEC) retraction activity (Hong *et al*., 2018). Luteolin induces apoptosis in cancerous tissue. It exerts cytotoxicity by modulating the activity of phosphatidylinositol 3′-kinase (PI3K)/Akt, NF-κB, X-linked inhibitor of apoptosis protein (XIAP), mitogenic protein c-Jun N-terminal kinase (JNK), tumor suppressor p53, and caspases (Lin *et al*., 2008). The anticancer activity of luteolin was tested on the hepatic carcinoma cell line SMMC-7721, BEL-7402. Treatment of luteolin arrests cell cycle at phase G1/S, the number of cells in the S phase decreased. The reciprocal picture was observed in pro and anti-apoptotic proteins. It upregulates the pro-apoptotic protein Bax and suppresses the anti-apoptotic protein Bcl-2 level. This event activates intrinsic caspase-3 mediated apoptosis (Ding *et al*. 2014).

Orientin: Orientin has similar effects to luteolin. The medicinal properties of orientin include antioxidant, antiviral, antibacterial, anti-inflammatory, cardioprotective, and neuroprotective (Lam *et al*., 2016). It has antioxidant activity and decreases the toxicity of H_2O_2 (Nayak *et al*., 2006). Orientin and vicenin both have antibacterial effects against *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus cohnii, Klebsiella pneumoniae,* and *Proteus*

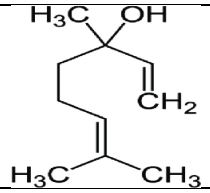
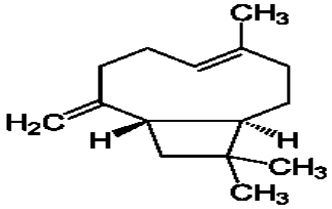
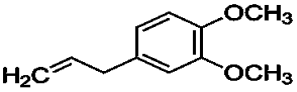
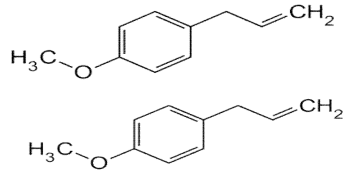
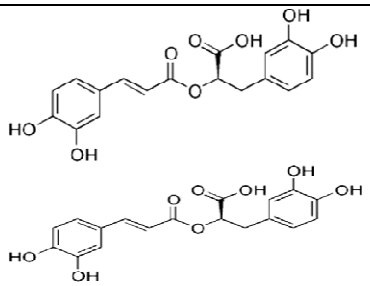
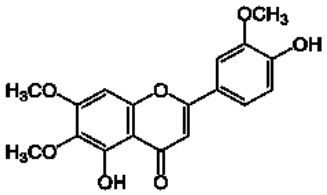
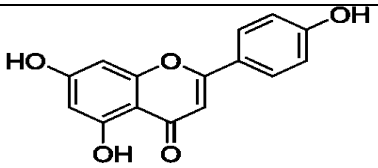
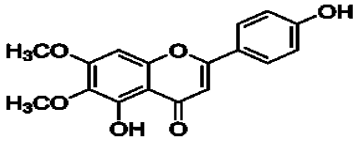
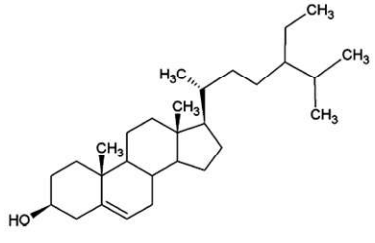
Table 2. The phytochemical components of *O. sanctum*, their characteristics and therapeutic importance

Phytochemical compounds and their general characteristics	Structure	Health benefits
Luteolin (Naturally-occurring flavonoid) Formula: $C_{15}H_{10}O_6$ Molecular Weight: 286.24 g/mol IUPAC name: 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-one Chemically it is a digitoflavone 3',4',5,7-Tetrahydroxyflavone Luteolin is a 3'-hydroxyflavonoid. It is a tetrahydroxyflavone which contains four hydroxy groups at the positions of 3', 4' 5 and 7 luteolin-7-olate(1-). It is a conjugate acid of a 2-(3,4-dihydroxyphenyl)-5-hydroxy-4-oxo-4H-chromen-7-olate.		Antioxidant, anti-inflammatory, and anti-cancer effects.
Orientin (Naturally-occurring water-soluble flavone) Formula: $C_{21}H_{20}O_{11}$ Molecular Weight: 448.4 g/mol IUPAC name: 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-[(2*S*,3*R*,4*R*,5*S*,6*R*)-3,4, 5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one Chemically it is a luteolin 8-C-glucoside, tetrahydroxyflavone and a 3'-hydroxyflavonoid. Orientin is a C-glycosyl compound which contains beta-D-glucopyranosyl moiety at position 8 luteolin.		Antioxidant, antiviral, antibacterial, anti-inflammatory, cardioprotective, and neuroprotective effects.
Vicenin2/ Violantin (A water-soluble flavonoid 8-c-glycosides) Formula: $C_{27}H_{30}O_{15}$ Molecular Weight: 594.5 g/mol IUPAC name: 5,7-Dihydroxy-2-(4-hydroxyphenyl)-6,8-bis[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl]-4H-chromen-4-one Chemically it is 6,8-di-C-glucosylapigenin The carbohydrate moiety is C-glycosidically linked to 8-position of a 2-phenylchromen-4-one flavonoid backbone.		Anti-inflammatory, and anti-cancer effects.
Serpentine (An indole alkaloid, a member of quinolizines) Formula: $C_{46}H_{56}N_4O_{10}$ Molecular Weight: 349.4 g/mol IUPAC name: methyl (15*R*,16*S*,20*S*)-16-methyl-17-oxa-3-aza-13-azoniapentacyclo[11.8.0.0^{2,10}.0^{4,9}.0^{15,20}]henicosa-1(13),2(10),4,6,8,11,18-heptaene-19-carboxylate Serpentine is an indole alkaloid. It derives from a hydride of a 18-oxayohimban It is 8- oxayohimban dehydrogenated at positions 3, 4, 5, 6, 16 and 17 and substituted by a methyl group at the 19alpha position and by a methoxycarbonyl group at position 16. It is a conjugate base of a serpentine(1+).		Serpentine has anti-hypertensive effect.
Quinine (A natural alkaloid) Formula: $C_{20}H_{24}N_2O_2$ Molecular Weight: 324.4 g/mol IUPAC name: (5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl)-(6-methoxyquinolin-4-yl)methanol.		Anti-malarial and muscle reluctant effects.
Rescinnamine (A natural alkaloid) Formula: C35H42N2O9 Molecular Weight: 634.7 g/mol IUPAC name: methyl (1R,15S,17R,18R,19S,20S)-6,18-dimethoxy-17-[(E)-3-(3,4,5-trimethoxyphenyl)prop-2-enoyl]oxy-1,3,11,12,14,15,16,17,18,19,20,21-dodecahydroyohimban-19-carboxylate Rescinnamine is a methyl ester, an organic heteropentacyclic compound and an indole alkaloid.		Anti-hypertensive effect.

Coninue ...

Tannin (A class of water-soluble polyphenolic biomolecules) Formula: $C_{76}H_{52}O_{46}$ Molecular Weight: 1701.2 g/mol IUPAC name: [2,3-dihydroxy-5-[[(2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5,6-tetrakis[[3,4-dihydroxy-5-(3,4,5-trihydroxybenzoyl)oxybenzoyl]oxy]oxan-2-yl]methoxycarbonyl]phenyl] 3,4,5-trihydroxybenzoate Polyphenolic compounds with molecular weights of around 500-3000 daltons and containing enough hydroxyl groups. There are two main types hydrolyzable tannins and condensed tannins.		Anti-inflammatory, and anti-cancer effects.
Limonene Formula: $C_{10}H_{16}$ Molecular Weight: 136.23 g/mol IUPAC name: 1-Methyl-4-(prop-1-en-2-yl)cyclohex-1-ene Limonene (+/-) is a racemic mixture of limonene, a natural cyclic monoterpene.		Anti tumorigenic activities. .
Eugenol Formula: $C_{10}H_{12}O_2$ Molecular Weight: 164.2 g/mol IUPAC name: 2-Methoxy-4-(prop-2-en-1-yl)phenol Chemically it is 4-Allyl-2-methoxyphenol 4-allylguaiacol. Eugenol is a phenylpropanoid, a monomethoxybenzene and a member of phenols. It derives from guaiacol with an allyl chain substituted para to the hydroxy group.		Antimicrobial, antioxidant, and anti-inflammatory activities.
Sesquiterpine Formula: $C_{19}H_{26}O_8$ Molecular Weight: 406.5 g/mol IUPAC name: 3-acetyloxy-6-hydroxy-3,6,9-trimethyl-2-oxo-4,5,6*a*,7,9*a*,9*b*-hexahydro-3*aH*-azuleno[4,5-b]furan-4-yl) (*E*)-2-methylbut-2-enoate It is a C15-terpenoids. it is the part of essential oils and made from three isoprene units.		Anti-inflammatory and analgesic agent.
Ursolic acid Formula: $C_{30}H_{48}O_3$ Molecular Weight: 456.7 g/mol IUPAC name: 1*S*,2*R*,4*aS*,6*aR*,6*aS*,6*bR*,8*aR*,10*S*,12*aR*,14*bS*)-10-hydroxy-1,2,6*a*,6*b*,9,9,12*a*-heptamethyl-2,3,4,5,6,6*a*,7,8,8*a*,10,11,12,13,14*b*-tetradecahydro-1*H*-picene-4*a*-carboxylic acid Ursolic acid is a ubiquitous triterpenoid. It is a pentacyclic triterpene acid.		Antimicrobial, antioxidant, and anti-inflammatory aeffects
Carvacrol (naturally occurring phenolics)., Formula: $C_{10}H_{14}O$ Molecular Weight: 150.22 g/mol IUPAC name: 2-methyl-5-propan-2-ylphenol Carvacrol is a phenol. Chemically it is a 5-Isopropyl-2-methylphenol. It is a natural monoterpene derivative of cymene. It is the major constituent of essential oils of *O. sanctum.*		Anti0bacterial agent

Continue …

Linalool Formula: $C_{10}H_{18}O$ Molecular Weight: 154.25 g/mol IUPAC name: 3,7-dimethylocta-1,6-dien-3-ol Linalool is tertiary alcohol and a monoterpenoid. It is a component of volatile oil of *O. sanctum* and gives fragrance. It is an octa-1-6diene substituted by methyl groups at positions 3 and 7 and a hydroxy group at position 3.		Opioidergic,analgesic anti-inflammatory, anti-carcinogenic and anti-microbila effects
Caryophyllene Formula: $C_{15}H_{24}$ Molecular Weight: 204.35 g/mol IUPAC name: (1*R*,4*E*,9*S*)-4,11,11-Trimethyl-8-methylidenebicyclo[7.2.0]undec-4-ene Caryophyllene is chemically called beta-caryophyllene in which the stereocentre adjacent to the exocyclic double bond has S configuration while the remaining stereocentre has R configuration. Caryophyllene is commonly present in essential oils.		.Anti-inflammatory, analgesic, antioxidant, and oncosataic effects
Methyl eugenol Formula: $C_{11}H_{14}O_2$ Molecular Weight: 178.23 g/mol IUPAC name: 1,2-dimethoxy-4-prop-2-enylbenzene Methyleugenol is present in essential oils.		Antioxidant
Estragole (Components of essential oil) Formula: $C_{10}H_{12}O$ Molecular Weight: 148.2 g/mol IUPAC name: 1-Methoxy-4-(prop-2-en-1-yl)benzene Chemically it is a 1-Allyl-4-methoxybenzene p-Allylanisol. It is the component of essential oils.		Potent antimicrobial agent
Rosmarinic acid (Naturally occurring phenolics) Formula: $C_{18}H_{16}O_8$ Molecular Weight: 360.3 g/mol IUPAC name: (2*R*)-3-(3,4-dihydroxyphenyl)-2-[(*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxypropanoic acid		Antioxidant, anti-inflammatory, and neuroprotective agent
Cirsilineol Formula: $C_{18}H_{16}O_7$ Molecular Weight: 344.3 g/mol IUPAC name: 5-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-6,7-dimethoxychromen-4-one. Cirsilineol is a trimethoxyflavone that is flavone substituted by methoxy groups at positions 6, 7 and 3' and hydroxy groups at positions 5 and 4' respectively.		Antineoplastic agent
Apigenin (Naturally occurring flavonoid) Formula: $C_{15}H_{10}O_5$ Molecular Weight: 270.24 g/mol IUPAC name: 5,7-Dihydroxy-2-(4-hydroxyphenyl)-4*H*-1-benzopyran-4-one Chemically, it is 5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one.		Anti-microbial, antioxidant, anti-carcinogenic, anti-inflammatory, and cardioprotective activity
Cirsimaritin (Naturally occurring flavone) Formula: $C_{17}H_{14}O_6$ Molecular Weight: 314.29 g/mol IUPAC name: 5-hydroxy-2-(4-hydroxyphenyl)-6,7-dimethoxychromen-4-one Chemically, it is 4',5-Dihydroxy-6,7-dimethoxyflavone 7-Methylcapillarisin It is a flavone substituted by methoxy groups at positions 6 and 7 and hydroxy groups at positions 5 and 4' respectively.		Anti-inflammatory, and anti-diabetogenic
Sitosterol (A phytosterol compound) Formula: $C_{29}H_{50}O$ Molecular Weight: 414.7 g/mol IUPAC name: 17-(5-Ethyl-6-methylheptan-2-yl)-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol Sitosterol is a class of phytosterols that is stigmast-5-ene substituted by a beta-hydroxy group at position 3. It is a derivative of stigmastane.		Antimicrobial, antioxidant, anti-inflammatory, anticancer, and anti-atherosclerotic
Source: https://pubchem.ncbi.nlm.nih.gov/compound/Rosmarinic-acid		

(Ali and Dixit, 2012). The antiviral property of orientin was also reported against Para 3 viruses and type 2 herpes simplex virus (Lam *et al*., 2016). Orientin ameliorates inflammatory activity by suppressing the NF-κB pathway along with the reduction of TNF-α, interleukin-6 (IL-6) release, and inactivating the extracellular regulated kinases (ERK) 1/2 (Lee *et al*., 2014), It modulates the high mobility group box-1 (HMGB1) protein, and endothelial cell protein C receptor (EPCR) to control inflammation (Yoo *et al*., 2014). Orientin increases NO levels in vascular smooth cells through activation of the cGMP pathway in hypertensive patients and decreases the risk factor for congestive heart failure (Fu *et al*., 2005). Orient protects the cardiac myocytes from apoptotic degeneration and increases the circulation rates in ischemic areas. It maintains mitochondrial integrity, prevents Bax, cytochrome c, and caspase-3 activation, and enhances anti-apoptotic protein Bcl-2 in the cardiomyocytes (Fu *et al*., 2006). Thus, orientin facilitates the survival of cardiac myocytes by promoting perfusion and reoxygenation rates in the ischemic area. Orientin suppresses oxidative stress and chronic inflammatory responses by avoiding the recruitment of macrophages and lymphocytes at the site of vascular inflammation. It lowers the high mobility group box-1 (HMGB1) protein levels and inhibits the function of the endothelial cell protein C receptor. Finally, orientin prevents vascular endothelial inflammation-induced atherosclerosis that is advantageous for the avoidance of vascular disorders (Brasier *et al*., 2002; Yoo *et al*., 2014).

Orientin has neuroprotective effects. It prevents Amyloid β-Protein (Aβ) induced Alzheimer's disease development in mice. Orientin reduces ROS and mitochondrial dysfunction. The advancement is the suppression of neural apoptosis and less accumulation of Aβ. The antioxidant activity protects oxidative stress-induced neurodegenerative disorders like Alzheimer's disease (Yu *et al*., 2015; Lam *et al*., 2016). Orientin is also an anti-carcinogenic agent. It exhibited cytotoxic effects in esophageal cancer EC109 cells (An *et al*., 2012) and MCF-7 breast cancer cells (Czemplik *et al*., 2016). Recently, Thangaraj *et al*. (2019) indicated that orientin arrest the cell cycle of HT29 colorectal carcinoma cells at the G0/G1 phase by modulating the cyclin and cyclin-dependent protein kinases. Orientin stimulates mitochondria-driven intrinsic apoptosis in carcinogenic cells, downregulates the levels of pro-apoptotic protein Bcl-2, and the tumor suppressor p-53.

Vicenin / Vicenin 2: The vicenin-2, vitexin, and luteolin exert cytoprotective effects against toxic drugs and carcinogens. Hepatic uridine diphosphate-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs) participate in the metabolism of many compounds such as hormones, neurotransmitters, drugs, and xenobiotic. UGTs and SULTs respectively transfer glucuronide and sulfonate groups from UDP-glucuronic acid and 3'-phospho-5'-adenylyl sulfate (PAPS) to the xenobiotic substances during Phase II conjugation reactions for their detoxification; these activities promote their renal excretion rates. The antioxidant effects of vicenin-2 and luteolin protect the hepatocytes from the toxicity drugs and exogenous substances (Chang *et al*., 2020). Vicenin suppresses inflammatory response by preventing the nuclear translocation of NF-κB and also decreases NO and TNF-α levels (Marrassini *et al*., 2011). Like other flavonoid compounds, vicenin-2 has anti-neoplastic effects. The treatment of vicenin-2 in combination with docetaxel (DTL) efficiently controls proliferation, angiogenesis, promotes apoptosis in *in vivo* state and in different prostate carcinoma cells like PC-3, DU-145, and LNCaP irrespective of their androgen sensitivity. The oncostatic action is mediated by suppression of the EGFR/Akt/mTOR/p70S6K pathway as well as downregulation of c-Myc, cyclin D1, cyclin B1, CDK4, PCNA, and hTERT activity. Vicenin-2 also prevents metastasis by increasing E-cadherin at the cell junction (Nagaprashantha *et al*., 2011).

Quinine: Quinine protects from malarial infection. It is a weak base, interferes with the breakdown and digestion of hemoglobin in malarial parasites. Quinine inhibits heme polymerase in the food vacuoles of *Plasmodium* species. Inhibition of hemoglobin digestion leads to starvation in parasites and forms paracidal toxic components that form partially degraded hemoglobin. Thus, heme appears as a schizonticidal as well as gametocytocidal agent in malarial parasites. Quinine is also a mild antipyretic and analgesic beneficial to the common cold. It also prevents idiopathic muscle cramps because it has direct effects on muscle membrane and sodium channels. It is generally used to treat muscle cramps (Ruggenenti *et al*., 2008). About 80 years ago, it was reported that quinine treatment was applicable for the anticipation of leg cramps. Recently, Gisselmann *et al*. (2018) had shown that quinine binds with human muscle nicotinic acetylcholine receptors (AChR) and inhibits Ach-dependent response in a non-competitive manner. The inhibition of AChR diminishes voltage response and relaxes muscular activities.

Rescinnamine: Rescinnamine has an inhibitory effect against the angiotensin-converting enzyme (ACE). It exhibits long-duration anti-hypertensive effects. Hypertension is a common problem in old-age people. The renin-angiotensin system involves in long-duration hypertension. The angiotensin-converting-enzyme plays a crucial role in this pathway. ACE converts angiotensin I to angiotensin II. Rescinnamine competes with angiotensin I for binding with ACE. The binding of rescinnamine with ACE prevents the conversion of angiotensin I to angiotensin II; later is also the mediator of aldosterone release from the adrenal cortex. Thus, rescinnamine inhibits angiotensin II-mediated vasoconstriction as well as aldosterone-dependent salt water-retention effects. this competitive inhibition gives beneficial effects to regulate hypertension (DrugBank URL:https://www.drugbank.ca/drugs/DB01180).

Tannin: Tannin has anticarcinogenic effects. It is an antioxidant due to its polyphenolic characteristics. It scavenges oxygen-free radicals and protects against cellular oxidative damage, including lipid peroxidation. It also inhibits lipoxygenase, xanthine oxidase, and monoamine oxidase. The antioxidative property of tannin advances anticarcinogenic and antimutagenic activity (Okuda *et al*., 1992; Malaver *et al*., 2019). Tannin also exerts antimicrobial activities. The phenolic hydroxyl group of tannin binds to protein adhesions and promotes the rupture of the plasma membrane of microbes leading to microbial cell damage (Pereira *et al*. 2015).

Limonene: Limonene has anti-neoplastic properties. The metabolites of DL-limonene like perillic acid, dihydroperillic acid uroterpenol and limonene 1,2- diol can stop the growth of tumors by inhibiting the p21-dependent signaling pathway. It induces apoptosis by activating the transforming growth factor-beta (TGF-β) signaling pathway. It also promotes the expression of apoptosis-related genes. It has the ability to arrest

the cell cycle at the G1 phase by reducing the expression cyclin and its post-translational modification (National Cancer Instititute URL: https://www.cancer.gov/ publications/ dictionaries/cancer-drug/def/limonene).

Eugenol: Eugenol shows potent antimicrobial, antioxidant, and anti-inflammatory activities (Marchese *et al*., 2017). It gives potential protective effects against microbial infection. Eugenol exerts a cytotoxic effect through the formation of a reactive intermediate, possibly a quinone methide, and promotes the killing of microbes (Bolton, 2014). Eugenol is effective against huge numbers of bacteria (both Gram-positive and Gram-negative) and fungi. The antimicrobial action of eugenol is mediated by multiple ways. It alters the membrane fatty acids that increase the instability of membrane, finally membrane damage followed by enhancement of non-specific permeability. It increases intracellular ROS production and also affects ATP synthesis (see review Marchese *et al*., 2017). Eugenol also inhibits few microbial enzymes like protease, histidine carboxylase, amylase, and ATPase (Hyldgaard *et al*., 2012).

The anti-fungal effects of eugenol are exerted by ROS-dependent lipid peroxidation, membrane disruption, and inhibition of H^+-ATPase (Marchese *et al*., 2017). Das *et al*. (2016) reported that eugenol treatment is effective against methicillin-resistant *S. aureus*. Eugenol increases intracellular ROS production after its entry within the microbes leading to cytotoxicity. It is suggested that ROS generation disrupts the bacterial plasma membrane as well as the electron transport chain (Su *et al*., 2009). Moreover, ROS has also an impact on bacterial DNA damage (Apolónio *et al*., 2014). Besides antibacterial effects, eugenol has anti-genotoxic, anti-inflammatory, and anticancer activities. The anti-inflammatory effect of eugenol is exerted by inhibition of 5-lipoxygenase resulting in decreased production of leukotrienes which is essential for the recruitment of polymorphonuclear leukocytes (PMNL) in the inflammatory response (Raghavenra *et al*., 2006). Eugenol has cytoprotective and antioxidant effects. it decreases cytochrome P4502E1 activity, lipid peroxidation, pro-inflammatory cytokines levels, and cyclooxygenase-2 expression in thioacetamide (TA)-induced hepatic injury in male Wistar rats (Yogalakshmi *et al*., 2010). Eugenol-induced anti-carcinogenesis has several mechanisms. Eugenol suppresses c-Myc, H-ras, and Bcl2 expression and promotes the expression of proapoptotic factors P53, Bax, and Caspase-3 in DMBA croton oil-induced skin carcinoma (Pal *et al*., 2010). Eugenol enhances the translocation of aryl hydrocarbon receptor (AhR) to the nucleus and upregulates the expression of cytochrome P-450 1A1 and AhR repressor; alternatively, inhibits the expression of G1 phase cell cycle-related retinoblastoma protein (Rb) in human HaCaT keratinocytes (Kalmes and Blömeke, 2012). Manikandan *et al*. (2011) suggested that eugenol decreases NF-κB activity and also downregulates NF-κB associated gene expression in N-methyl-N'-nitro-N-nitrosoguanidine (MNNG)-mediated gastric tumors.

Sesquiterpene: Sesquiterpene is the component of essential oils. It shows potent anti-inflammatory, analgesic, and antimicrobial activity. It exerts antigenotoxic, antimutagenic, and anticancer effects (Sharma *et al*., 2013b).

Ursolic acid: Ursolic acid is a competent antimicrobial agent. It actively inhibits the growth of almost all pathogenic microorganism including bacteria (Gram-positive, Gram-negative, and mycobacterium), fungi, virus (hepatitis C, herpes simplex), protozoa (leishmania, plasmodium, Trypanosoma), and nematodes (*Brugia malayi*, *Wuchereria bancrofti*) (Woźniak *et al*., 2015). Ursolic acid exhibits anti-inflammatory, antioxidant, anti-carcinogenic, anti-diabetic, cardioprotective, neuroprotective, hepatoprotective actions. Ursolic acid has antioxidant properties that scavenge ROS. It enhances the activity of antioxidant enzymes including SOD CAT, GR, GPx, and reduced glutathione (GSH) levels. Ursolic acid prevents cancerous growth in different ways. It protects various cancers such as skin, colon, breast, cervical, ovaries, pancreas, and liver. It inhibits the invasion of tumor cells by reducing the expression of matrix metalloproteinase-2, 9. The structure of ursolic acid is very similar to synthetic glucocorticoids like dexamethasone. It is suggested that ursolic acid down-modulates the trans-activating function of AP-1 proteins dependent matrix metalloproteinase-9 (MMP-9) promoter region as like glucocorticoid system. Ursolic acid suppresses NF-κB-mediated activation by blocking the DNA binding capacity of heterodimeric (p50 and p65) NF-κB.

It blocks the degradation of I-κBα by inactivating kappa kinase-mediated phosphorylation of I-κB as well as inhibition of phosphorylation of p65. These actions suppress the nuclear translocation of NF-κB and induction of NF-κB dependent reporter gene. The result is inhibition of expression of TNFα, IL6, cyclin D1, COX-2, and MMP-9. Ursolic acid also inhibits COX-2 activity and prostaglandin E2 (PGE2) synthesis. To stop apoptosis, ursolic acid decreases Bcl 2/xL, ERK1/2, mitochondrial membrane potential whereas it increases p53, p21, Cyt c levels, JNK, and caspase activity. Ursolic acid protects different organs from tissue toxicity. It has cardio-protective and anti-hypertensive effects. It increases nitric oxide (NO) production and inhibits ACE activity as anti-hypertensive functions. Ursolic acid controls the local ischemia and protects cardiac myocytes. It preserves redox homeostasis by scavenging free radicals and maintaining the activity of SOD, CAT, GR, and GPx. Moreover, it rescues cardiac cells from injury by decreasing TNFα, Cyt c levels, and inactivation of caspases. Ursolic acid exerts neuroprotective actions.
The antioxidant activity is very similar to the cardiac system. Ursolic acid protects the neurons and astrocytes from inflammation. It downregulates NF-κB mediated expression of COX-2, iNOS, TNFα, IL-1β, Il-6, and (PGE2 synthesis. It blocks mitochondrial dysfunction and caspase (3/9) activation. To regulate the intracellular environment, it enhances PI3K/p-Akt, PPARγ actions and decreases FoxO1 and MMP2/9 activity. Thereby, ursolic acid provides a defensive measure against neurodegeneration. The liver is the metabolic factory of the body. In the hepatic environment, ursolic acid reduces ROS-mediated damage, prevents apoptosis, lipid accumulation, inflammatory response. Diabetes is a serious problem throughout the world. Ursolic acid exerts several strategies against diabetes. It increases insulin sensitivity and glucose utilization in skeletal muscle. It elevates plasma insulin levels, expression and activity of GLUT4 and insulin receptors, glycogen synthesis, lipid utilization, and modulation of PPARγ and aP2 activity [see review Woźniak *et al*. (see review Woźniak *et al*., 2015 and Seo *et al*., 2018). Thus, ursolic acid can protect the body from oxidative stress, inflammatory response, metabolic disorders, and carcinogenesis.

Carvacrol: Carvacrol is treated as an antimicrobial, antioxidant, and anticancer agent. The potent antimicrobial action of carvacrol was observed against both Gram-positive (different species of *Staphylococcus,* and *Streptococcus B.*

cereus) Gram-negative bacteria (*E. coli, Salmonella, Helicobacter pylori*), and *Mycobacterium tuberculosis* and *bovis* as well as fungi. It is also effective against antibiotic-resistant pathogenic bacteria (Mohammad *et al*., 2017; Marinelli *et al*., 2018). Several mechanisms had been suggested about the antibacterial activity; these include alteration of membrane structure, interruption of nucleic acids synthesis and functions, impaired metabolism, leakage of cytoplasmic constituents, and quorum sensing (QS) inhibition. Carvacrol alters the characteristics of membrane fatty acids resulting rise in membrane fluidity and permeability which favor the release of essential intracytoplasmic constituents. Carvacrol-induced cytosolic consequences are depletion of intracellular ATP pool, changes membrane potential, imbalance of intracellular pH, and potassium efflux due to leakiness of the membrane. Gram-negative bacteria have a unique structure of the outer membrane. Like cytoplasmic membrane, carvacrol increases the permeability of the outer membrane in *E. coli* O157:H7. It also increases heat shock proteins 60 (HSP60) levels and exerts a negative impact on flagellar protein synthesis to increase the numbers of non-motile cells. Thus, carvacrol ultimately gives a bactericidal effect for both Gram-positive and Gram-negative bacteria (Marinelli *et al*., 2018). Carvacrol exhibits oncostatic action by influencing the induction of the proapoptotic pathway (Sharifi-Rad *et al*., 2018).

Linalool: Linalool (monoterpene compound) has an effect on the brain neurotransmitters glutamic acid, γ-aminobutyric acid (GABA), acetylcholine, and dopamine. The effect is opioidergic and reduction of pain response (Pereira *et al*., 2018). Linalool is metabolized in the body, produces oxygenated linalool metabolites at carbon 8 as well as hydroxylated or carboxylated metabolites at carbon 8. However, only oxygenated linalool metabolites overexpressed α1β2γ2 GABA receptors and potentially affects the GABAergic currents; other metabolites have no significant effects (Milanos *et al*., 2017). Linalool possesses anti-inflammatory effects. Several researchers indicated that linalool regulates the activity of inflammatory cells and diminishes the NF-κB mediated expression of TNF-α, IL-6, IL-1β, IL-8, and MCP-1 (Huo *et al*., 2013; Ma *et al*., 2015). Linalool also inhibits NO synthesis and COX-2 dependent PGE2 production (Pereira *et al*., 2018). The anticancer activity of linalool was tested on various cancer cell lines (e.g. DU145 and PC-3 human prostate cancer cells, U937 myeloid leukemia cells, HeLa cells, RPMI 7932 human melanoma cells, etc.). It arrests cell cycle in G0/G1 or G2/M phase, inhibits the expression of p53, p21, p27, p16, and p18 and cyclin-dependent kinases inhibitors (CDKIs) genes. The induction of apoptosis is an important part of cancer prevention. Linalool promotes the activity of pro-apoptotic factors (Bax and Bak) and reduces anti-apoptotic factors (Bcl-2 and Bcl-xl) (Chang *et al*., 2015; Pereira *et al*., 2018). Gunaseelan *et al*. (2016) reported that linalool blocks NF-κB activation and suppresses the expression of TNF-α, IL-6, COX-2, VEGF, and TGF-β1.

The nociceptive response is driven by pro-inflammatory cytokines IL-1β and TNF-α. They trigger the liberation of glutamate and substance P from nerve endings. Glutamate binds with NMDA receptors and stimulates pain response. Linalool inhibits pro-inflammatory cytokines-induced NMDA receptor activation for analgesic effects (Batista *et al*., 2010). Linalool is an antimicrobial agent, effective against both bacteria (*Pseudomonas aeruginosa*, *Escherichia coli,* and *Staphylococcus aureus*) and fungi *(Candida albicans* and *Aspergillus brasiliensis*) (Herman *et al*., 2016). Moreover, linalool has antioxidant properties. Thus, it protects oxidative stress-induced several pathological conditions like neurological disorders, atherosclerosis, high blood pressure, ischemia/perfusion, diabetes, acute respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), and asthma (Birben *et al*., 2012).

Caryophyllene: Caryophyllene/β-caryophyllene is a natural bicyclic sesquiterpene, belongs to the cannabinoid family. Caryophyllene has anti-inflammatory, analgesic, antioxidant, antiviral, oncosataic, neuroprotective properties (Fidyt *et al*., 2016; Francomano *et al*., 2019). Cannabinoids act through two receptors and CB2-R. Caryophyllene has a high affinity to CB2-R but not CB1-R. CB2-Rs are mainly present in peripheral tissues, immune-competent cells, and to a lesser extent in the central nervous system (Fidyt *et al*., 2016). Both receptors are G-protein coupled receptors. The binding of caryophyllene with CB2-R activates $G_{i/o}$ subunit that inhibits adenylyl cyclase function leading to a decline of cAMP production. The $G_{\beta\gamma}$ subunit of activated G-protein stimulates both mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling pathways (Demuth and Molleman, 2006). Caryophyllene acts like a non-steroidal anti-inflammatory. The anti-inflammatory action of BCP has mainly occurred through the inhibition of inducible nitric oxide synthase (iNOS) and NF-κB activity. The result is the regulation of TNF-α, IL-6, and IL-1β levels and COX-2 activity for lowering PGE2 synthesis (Chang *et al*., 2013; Hu *et al*., 2017; Francomano *et al*., 2019). Regulation of inflammatory mediators is also associated with analgesic actions. Moreover, caryophyllene increases the release of beta-endorphin which acts through μ-opioid receptors to reduce the pain (Katsuyama *et al*., 2013). The anticancer effect is very similar to other bioactive compounds. Caryophyllene decreases Bcl-2/xL, IAP-1/2 and increases caspases activity for apoptosis, arrest cell cycle by regulating cyclin levels, reduces VRGF for anti-angiogenesis, inhibits PI3K/mTOR/Akt pathway to prevent the carcinogenesis (Yamaguchi and Levy, 2016; Pavithra *et al*., 2018; Fidyt *et al*., 2016). Caryophyllene has preventive measures against Parkinson's disease, Alzheimer's disease. It acts through CB2/Nrf2 pathway to inhibit ROS production, mitochondrial disability, maintains redox homeostasis, prevents apoptosis by regulating pro-apoptotic (Bax and caspase-3) and anti-apoptotic (Bcl-2) factors, inhibit phosphorylation of JNK (c-Jun N-terminal Kinase) decrease the production of inflammatory cytokines like IL-1β, IL-6, and TNF-α (Viveros-Paredes *et al*., 2017; Wang *et al*., 2018; Francomano *et al*., 2019). Thus, caryophyllene potentially fights against inflammation-mediated neurodegenerative disorders.

Methyl eugenol: Methyl eugenol has antioxidant, anti-inflammatory, and antimicrobial properties. It is active against a variety of microbes (Gogoi *et al*. 2020).

Estragole: Estragole has antioxidant (Morais *et al*., 2006), anti-inflammatory activity (Ponte *et al*., 2012), and antimicrobial activities. It is a potent anti-fungal agent, effective against various fungi like *Aspergillus niger, A. japonicus, A. oryzae, Fusarium oxysporum*, *Rhizophus oryzae* and *R. stolonifer.* The anti-bacterial effect was also observed for Gram-positive bacteria (*Enterococcus faecalis*, *Staphylococcus epidermidis,* and *S. aureus*) and Gram-negative bacteria (*Escherichia coli, Morganella morganii, Proteus*

mirabilis, *Salmonella enteritidis, S. entiritidis serovar typhimurium, Pseudomonas aeruginosa*) (Mota *et al*., 2015; Song *et al*., 2016).

Rosmarinic acid: Rosmarinic acid has different pharmacological functions like anti-inflammatory, antioxidative, anti-apoptotic, and anti-tumorigenic effects (Kang *et al*., 2003; Luo *et al*., 2020). The anti-inflammatory action of rosmarinic acid is due to the presence of the free phenolic group. It affects the complement-dependent inflammatory response. Rosmarinic acid inhibits the complement pathway through inactivation of C3-convertase and prevents cleavage of C5 which is advantageous at the terminal attack sequence. This inhibitory effect is protective against complement-mediated pathogenesis (Peake *et al*. 1991). Rosmarinic acid also suppresses TCR (T cell receptor) signaling and NF-AT (nuclear factor of activated T cells) dependent IL-2 expression. Basically, rosmarinic acid modulates IP_3-induced calcium release and activity of phospholipase C-gamma 1 leading to suppression of NF-AT functions (Kang *et al*., 2003). This indicates ad additional route of anti-inflammatory effect. Acute inflammation and chronic inflammation are significantly associated with human health (Yi *et al*., 2017). Rosmarinic acid is a potent inhibitor of inflammatory diseases. Rosmarinic acid critically modulates the impacts of several cytokines (IL-1β, IL-4, IL-5, IL-6, IL-13, IL-22, TNF-α, and IFN-γ) either reducing their activity or by suppressing their expression. It directly inhibits the expression of NF-κBp65, iNOS, and COX-2 resulting in diminution of NF-κB dependent activation, NO production, and PGE2 synthesis. It controls toll like receptor 4 (TLR4) responses and also reduces the expression and activation of myeloperoxidase (MPO). Moreover, rosmarinic acid controls the activity of macrophage inflammatory protein-2 (MIP-2) to inhibit the infiltration of polymorphonuclear leukocytes (PMNLs) at the inflammatory sites. These multidimensional anti-inflammatory effects have beneficial impacts on the different inflammatory diseases like arthritis, colitis, atopic dermatitis, asthma, allergic rhinitis, acute pancreatitis, and mastitis (see review Luo *et al*., 2020). Moon *et al*. (2010) suggested that rosmarinic acid can be applied for the treatment of cancer. It prevents TNF-α mediated NF-κB activation by inhibiting the phosphorylation and degradation of I-κBα, resulting in the prevention of translocation of p50 and p65 subunit of NF-κB to the nucleus. This inhibition reduces the NF-κB-mediated expression of anti-apoptotic factors (IAP-1, IAP-2, and XIAP). However, rosmarinic acid activates caspase-dependent apoptosis by dropping the mitochondrial potential and increasing cytosolic cytochrome c levels. Rosmarinic acid was established as a neuroprotective agent and improves amyloid β induced Alzheimer's disease. Rosmarinic acid increases monoamines (norepinephrine, dopamine, 3,4-dihydroxyphenylacetic acid) levels in the cerebral cortex and also decreases the breakdown of monoamines particularly dopamine by inhibiting monoamine oxidase B (Maob). Additionally, Rosmarinic acid suppresses the expression of the gene *Maob*. Maintenance of brain monoamines levels prevents generation and accumulation of amyloid β resulting in inhibition of progression of Alzheimer's disease (Hase *et al*., 2019).

Cirsilineol: Cirsilineol is an antineoplastic agent and prevents cancer. The *in vitro* study shows that it significantly inhibits the proliferation of pf different cancer cells (Caov-3, Skov-3, PC3, and Hela). It acts as an apoptosis-inducing agent by changing the mitochondrial membrane potential, subsequently liberation of cytochrome c, and activation of caspases 3 and 9. Cirsilineol has the ability to activate poly (ADP-ribose) polymerase (PARP) further progression of apoptosis (Sheng *et al*., 2010). Yin *et al*. (2008) reported that cirsilineol has immunosuppressive effects and significantly inhibits T cell proliferation.

Apigenin: Apigenin exhibits anti-microbial, antioxidant, anti-mutagenic, anti-carcinogenic, anti-inflammatory, and anti-proliferative activity (Patel *et al*., 2007). The antioxidant activity of apigenin is due to the presence of a double bond between carbon 2,3 which makes the structure more reactive (Tripoli *et al*., 2007). Apigenin induces the expression of antioxidant enzymes such as glutathione synthase, CAT, and SOD to fight against cellular oxidative stress (Myhrstad *et al*., 2002; Salehi *et al*., 2019). Apigenin is a truly antimicrobial agent. It is active against numerous Gram-positive and Gram-negative bacteria, fungi, and most of the pathogenic viruses [enterovirus 71 (EV71), herpes simplex virus HSV-1 and HSV-2, hepatitis C virus, influenza virus, hand, foot, and mouth disease virus, and African swine fever virus (ASFV)] (Wang *et al*., 2019). The anti-bacterial effect is mediated by inhibiting nucleic acid synthesizing enzymes (DNA gyrase, topoisomerase IV, and RNA polymerase) and disrupts the cell wall/membrane formation by altering the activity of the d-Alanine ligase and type II fatty acid synthetic pathway (Yu *et al*., 2007, Wu *et al*., 2008, Wang *et al*., 2017; Wang *et al*., 2019). The causes of antifungal activity of apigenin are alteration of cell surface potential and release of intracellular components (Lee *et al*., 2018). Apigenin downregulates viral polyprotein expression, promotes ROS generation, and cytokines induced apoptosis of viral-infected cells. It also inhibits viral replication by counteracting the viral ribosomal activity and c-Jun N-terminal kinase (JNK) functions (Lv *et al*., 2014). It down regulates the expression of mature microRNA (Shibata *et al*., 2014). Apigenin exerts beneficial effects upon the vascular endothelium. It alters the conductance Ca^{2+}-activated K^+ channels [K(Ca)] causing hyperpolarization of the cells. This effect starts Ca^{2+} influx into the endothelial cells and increases nitric oxide (NO) production. It also exhibits antiangiogenic activity and endothelial cell proliferation by Akt dephosphorylation (Erdogan *et al*., 2007). These effects increase the perfusion rates of the tissues. Apigenin restricts the production of proinflammatory cytokines (IL-1β, IL-8, and TNF-α) and suppresses NF-κB mediated inflammatory activity. It also blocks the IKK activity and starts hypophosphorylation of p65 (Nicholas *et al*., 2007). It has the capacity to inhibit cyclooxygenase-2 (COX-2) expression, NO synthesis, and monocyte adherence. All these activities significantly decrease inflammatory response Lee *et al*., 2007). Apigenin shows anticancer activity. It inhibits the phosphorylation of the p38 and PI3K-Akt pathways. It arrests the cell cycle at G0/G1 or G2/M phase. It significantly decreases cyclin D1, D2, E, A, and B and their regulatory partners CDK 2, 4, and 6 expressions. It induces apoptosis by activating caspase-3 and 9. Apigenin enhances the stability of the tumor suppressor factor p53 (Salehi *et al*., 2019). Apigenin has comprehensive regulation on PI3K/AKT, MAPK/ERK, JAK/STAT, NF-κB, and Wnt/β-catenin pathways associated with apoptosis, autophagy, immune response, cell cycle, and metastasis to control the cancer progression (see review Yan *et al*., 2017). Shukla and Gupta (2007) studied the anticancer effects of apigenin on human prostate cancer cells LNCaP and PC-3. Apigenin decreases the expression and phosphorylation of p38 and PI3K-

Akt, and retinoblastoma protein (Rb), causes marked reduction in cyclin D1, D2, and E levels and activation of their target kinases (CDK 2, 4, and 6) resulting in the arrest of the cell cycle. It increases phosphorylation of ERK1/2 and JNK1/2 followed by inhibition of c-FOS expression, suggesting the overall anticancer effects of apigenin. Apigenin blocks the intravasation of MDA-MB231 breast cancer spheroids by inhibiting MMP1 and by modulating the lymph endothelial cell (LEC) retraction activity (Hong *et al*., 2018). A recent review of Salehi *et al*. (2019) described the beneficial role of apigenin on diabetes, amnesia, Alzheimer's disease, depression, and insomnia. It decreases blood glucose levels and stimulates glucose-induced insulin secretion, improves memory formation, reduces fibrillar amyloid deposition, and β-amyloid peptide concentration, attenuates stress-induced brain monoamine synthesis. Apigenin inhibits the aldose reductase enzyme in the polyol pathway and prevents diabetogenic cataract formation (Rodriguez *et al*., 2018). Thus, apigenin has complete health promotional effects.

Cirsimaritin: Cirsimaritin inhibits lens aldose reductase and prevents cataract formation, but this inhibitory action weaker than apigenin (Rodriguez *et al*., 2018). Cirsimaritin exhibits anti-inflammatory effects. Cirsimaritin inhibits degradation of IκBα and activation of NF-κB as well as the synthesis of IL-6 and TNF-α. It prevents the expression of iNOS and NO production. It also regulates the activity of Akt and STAT3 suggesting a combinatorial consequence against inflammation (Shin *et al*., 2017).

Sitosterol/β-sitosterol: Sitosterol is a member of phytosterols. Pharmacologically, β-sitosterol involves numerous physiological functions like antimicrobial, antioxidant, anti-inflammatory, anticancer, and anti-atherosclerosis activities by avoiding systemic toxicity (Li *et al*., 2001; Ambavade *et al*., 2014). Several reports exhibited the anti-protozoal, anti-bacterial, and anti-fungal effects of β-sitosterol (Ajaiyeoba *et al*., 2003; Li *et al*., 2008; Sayeed *et al*., 2016). Sitosterol inhibits the activity of sortase enzymes which belong to specific transpeptidases essential for anchoring the virulence factor on the surface of the bacteria (Kanokmedhakul *et al*., 2005). Sitosterol increases the activity of SOD and CAT, maintains GSH levels in cells to minimize the OS (Vivancos and Moreno, 2005). Regulation of inflammatory response is the crucial part; β-sitosterol inhibits neutrophil migration and extravasation into inflamed tissues. It also decreases myeloperoxidase releases and prevents the degranulation of leukocytes. Moreover, sitosterol blocks the phosphorylation of NF-κB and downregulates the expression Il-6, IL-8, and TNF-α (Ambavade *et al*., 2014). Sitosterol induces apoptosis in cancerous tissue. The anti-carcinogenic effects of sitosterol were tested on MCF-7 and MDA-MB-231 human breast cancer cells, human leukemic U937 cells, and HT-29 colon carcinoma cell lines. β-sitosterol mostly stimulates caspases-induced apoptosis, it also increases the Bax/Bcl-2 ratio (Saeidnia *et al*., 2014). Treatment of β-sitosterol to MDA-MB-231 human breast cells enhances caspase-dependent program cell death. β-sitosterol maximally increases the activities of caspases 8 and 9 in comparison to caspase 3 (Awad *et al*., 2003). It also downregulates the activity of ERK1/2 and activates apoptotic signals in MCF-7 breast cancer cells (Tasyriq *et al*., 2012). Sitosterol cannot be converted to testosterone and has inhibitory effects on aromatase and 5-alpha-reductase. Thus, sitosterol is beneficial to improve the complications of benign prostatic hyperplasia (Rakel, 2018). β-sitosterol is the prevalent plant sterol and very similar to cholesterol as an animal body. It is also synthesized from the mevalonic acid pathway in plant cells but acts as an anti-hyperlipidemic and anti-cholesteric agent. This phytosterol counteracts cholesterol metabolism. Sitosterol is poorly absorbed in the intestine but interferes with the lymphatic absorption of cholesterol. It effectively lowers serum LDL-cholesterol that reduces the risk of atherosclerosis and also decreases the survival of cancer cells by inhibiting the supply of sterol to the proliferating tumor cells. Alternatively, it increases HDL-cholesterol in the blood and promotes the excretion of cholesterol through bile (Ambavade *et al*., 2014). Sitosterol prevents the activation of NF-κB and also reduces the expression of vascular adhesion and intracellular adhesion molecule 1 in TNF-alpha-stimulated human aortic endothelial cells (HAEC) leading to restriction of the inflammatory response (Loizou *et al*., 2010). Thus, antioxidant capacity, anti-inflammatory, and anti-cholesteric effects prevent the formation of the atherosclerotic plug. β-sitosterol restricts oxidative stress-induced damage and neurotoxicity (Brimson *et al*., 2012). It enhances the expressions of some angiogenic proteins (Von Willebrand factors, VEGF VEGF receptor, and blood vessel matrix laminin) to improves ischemic-related damage in the brain (Choi *et al*., 2002). It was also suggested that sitosterol binds with $GABA_A$ receptors to modulate brain functions (Sayeed *et al*., 2016).

CONCLUSION

From the Vedic era to the modern civilized world, *O. sanctum* is used as traditional medicine. This plant is an example of holistic Ayurvedic medicine for the vast array of health benefits (Fig.2) and to be the solution of many types of modern-day health problems. The extract of tulsi contains several biopharmaceutical compounds. Different pharmacological studies had established the scientific basis of its applications. The antibacterial, anti-inflammatory, ulcer healing, antioxidant, immune-modulatory properties are the fundamental basis of its mode of action. In the future, this type of medicinal plant will be the route of alternative medicine to prevent the toxicity of chemical drugs and also will be the solution for the treatment of diseases that are still in a complicated situation.

Figure 2. Multipurpose health benefits of of tulsi (*Oscimum sanctum* Linn.)

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ABBREVIATION

ACE: angiotensin-converting enzyme; Akt: protein kinase B; aP2: activating protein 2; Bax: bcl-2-like protein 4; Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma-extra large; CAT: catalase; CDK: cyclin dependent kinase; COX-2: cyclooxygenase-2; EGFR: epidermal growth factor receptor; EPCR: endothelial cell protein C receptor; ERK: extracellular signal-regulated kinase; FoxO1: Forkhead box protein O1; GLUT1: glucose transporter 1; GLUT4: glucose transporter 4; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: reduced glutathione; GST: glutathione S-transferase; HMGB1: high mobility group box-1; HO-1: heme oxygenase; IAP: inhibitor of apoptosis; IKK: inhibitory kappa kinase; IL: interleukin; iNOS: inducible nitric oxide synthase; IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; JNK: c-Jun N-terminal kinase; LEC: lymph endothelial cell; LPO: lipid peroxidation; MAPK: mitogen-activated protein kinases; MMP: matrix metalloproteinase; mTOR: mammalian target of rapamycin; OS: oxidative stress; NF-κB: nuclear factor kappa-lightchain-enhancer of activated B cells; NMDA: N-methyl D-aspartate; NO: nitric oxide; Nrf2: nuclear factor E2-related factor 2; p-Akt: phosphorylated protein kinase B; PCNA: proliferating cell nuclear antigen; PGE2: prostaglandinE2; PI3K: phosphoinositide 3-kinase; PMNLs: polymorphonuclear leukocytes; PPAR γ: peroxisome proliferator-activated receptor gamma; ROS: reactive oxygen species; SOD: superoxide dismutase; STAT: signal transducer and activator of transcription ; TGF-β: transforming growth factor beta; TLR: toll like receptor; TNF-α: tumor necrosis factor-alpha; VEGF: vascular endothelial growth factor.

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