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Review Article

A PHARMACOLOGICAL AND TOXICOLOGICAL REVIEW OF MATCHLESS HERB: TULASI

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ABSTRACT

Nature has many useful herbs and plants for human beings. A majority of world's population in developing countries still relies on herbal medicines to meet its health needs. Among the plants known for medicinal value, the plants of genus *Ocimum* belonging to family *Lamiaceae* are very important for their therapeutic potentials. *Ocimum sanctum* Linn. (Tulasi), a sacred and traditional medicinal plant of India which possesses innumerable health benefits and therefore regarded as the "Elixir of Life", 'Incomparable one' 'Machless one' and 'Queen of Herbs'. Many research and studies suggest that Tulasi may be a COX-2 inhibitor, like many modern painkillers, due to its significant amount of eugenol. Bioactive compounds of Tulasi responsible for its various medicinal properties and their effects at the molecular level need to be investigated in more detail for pharmaceutical therapeutic applications. The present review summarizes the comprehensive information concerning pharmacological activities such as analgesic, anti-inflammatory, antipyretic, antiulcer, antiarthritic, antiasthamatic, antibacterial, antifungal, antiviral, antihelmintic, antiplasmodic, larvicidal, antioxidant, antistress, anticancer, anticataleptic, anticataract, wound healing, anticoagulant,antioxidant, antidepressant, anticonvulsant, antidiabetic, antifertility, antihyperlipidemic, cardioprotective, antihypertensive, antitussive, antiemetic, genoprotective, hepatoprotective, diuretic, Immunomodulatory, neuroprotective, radioprotective activites along with toxicological studies.

Keywords: Tulasi, Ocimum sanctum, Lamiaceae, Pharmacological activities, Toxicological studies.

INTRODUCTION

Medicinal plants are the richest bio-resource of drugs for traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharamaceutical intermediates and chemical entities for synthetic drugs[1]. Medicinal plants have a very rich sources of secondary metabolites and oils which are of therapeutics importance. Some of the most important bioactive phytochemical constituents in plants are alkaloids, flavonoids, phenolics, essential oils, tannins and saponins. The important advantages of medicinal plants in various treatments are: their safety besides being less expensive, efficacy and availability through out the world[2]. Use of plants as a source of medicinal value is a very old concept. In India use of plants as a medicine appeared in Rigveda which has been written 3500 - 1600 B.C[3].

Properties of plants as a source of medicine were studied in detailed in Ayurveda, a system of traditional Hindu medicine which is native to India and is renowned as one of the major systems of alternative and complementary medicine. According to Hindu mythology, Dhanvantari, the physician of the God's, is attributed with the origin of ayurvedic medicine. Ayurveda traces its origin to the Vedas particularly Atharvaveda and it stresses the use of indigenous plant based medicines for the treatment of diseases[4].

Tulsi "Queen of herbs" is described as sacred and medicinal plant in ancient literature. It is an important symbol of the Hindu religious tradition. The name *Tulsi* is derived from *„Sanskrit"*, which means "matchless one"[5]. Its

other name, Vishnupriya means the one that pleases Lord Vishnu. This plant belongs to the family *Labiatae*, characterized by square stem and specific aroma. Botanical name of *Tulsi* is *Ocimum sanctum* (Linn). In India, the plant is grown throughout the country from Andaman and Nicobar islands to the Himalayas up to 1800 meters above the sea level[6]. It is also abundantly found in Malaysia, Australia, West Africa and some of the Arab countries. *Ocimum sanctum* (Linn) is the most prominent species of the genera. The leaves of the plant are considered to be very holy and often form a consistent part of the Hindu spiritual rituals (*Tirtha* or *Prasada*). *Ocimum sanctum* has two varieties i.e. black (*Krishna Tulsi*) and green (*Rama Tulsi*), their chemical constituents are similar. Both the varieties also have common medicinal properties[7].

There are many species of *Ocimum,* which have their different morphological or anatomical characters. They are found in different places and have different living conditions; so that they have different medicinal value. Content of secondarymetabolites also differs species to species. Different species of *Ocimum* are *Ocimum americanum*, *Ocimum basilicum*,*Ocimum campechianum*, *Ocimum centraliafricanum*, *Ocimumgratissimum*, *Ocimum kilimandscharicum*, *Ocimum minimum*,*Ocimum viride*, *Ocimum suave*, *Ocimum ovatum*, *Ocimumselloi*, *Ocimum tenuiflorum* and *Ocimum citriodorum* (*O.americanum* × *O. basilicum*)[8].

Fig. 1: Plant of *Ocimum sanctum* (Tulsi)

TAXONOMY

Kingdom : Plantae
Subkingdom : Tracheobionta
Superdivision : Spermatophyta
Division : Magnoliophyta
Class : Magnoliopsida
Subclass : Asteridae
Order : Lamiales
Family : Lamiaceae
Genus : Ocimum
Species : *O. sanctum*

Morphology

It is an erect, much branched, fragrant and erected plant attaining a height of about 30-60 cm when mature. Its aromatic leaves are simple, opposite, elliptic, oblong, obtuse or acute with entire or sub serrate or dentate margins, growing up to 5 cm long. The Tulsi flowers are small having purple to reddish color, present in small compact clusters on cylindrical spikes. Stalk less heart-shaped bracts are there at the base of each flower cluster. Sepal cup is not hairy within. Flowers are rarely longer than 5 mm, calyx tube bearded outside near base. Flower tube is hairy. The fruits are small and the seeds yellow to reddish in colour[9].

Table 1: Chemical constituents of *O. sanctum*

Plant Parts	Extracts	Chemical constituents
Leaves / areal parts[10-13]	Alcoholic extract	Aesculectin, Aesculin, Apgenin, Caffiec acid, Chlorgenic acid, Apigenin, Apigenin-o-glucuronide, Triacontanol ferulate, Vicenin-2, Circineol, Gallic acid, Galuteolin, Isorientin, Isovitexin, Isovitexin, Circineol, Luteolin, Molludistin, Orientin, Procatechuic acid, Stigmasterol, Urosolic acid, Vallinin, Viceni, Vitexin, Vllinin acid
Whole plant [14,11,12]	Vitamin and mineral contents	Vitamin C, Vitamin A, Vitamin E, Calcium, Phosphours, Chromium, Copper, Carotene, Zink, Iron, Nickel
Leaves [11-17]	Essential oil	Aromadendrene oxide, Benzaldehyde, Borneol, Bornyl acetate, Camphor, Caryophyllene oxide, cis-α-Terpineol, Veridifloro, Cubenol, Cardinene, D-Limonene, Eicosane, Eucalyptol, Eugenol, Methyl Eugenol, Farnesene, Farnesol, Furaldehyde, Germacrene, Heptanol, Humulene, Limonene, n-butylbenzoate, Ocimene, Oleic acid, Sabinene, Selinene, α-Camphene, α-Myrcene, α-Pinene, β-Pinene, α-Thujene, β-Guaiene, β-Gurjunene, Methyl Chavicol, Linalool, Cirsilineol, Circimaritin phytol, Isothymusin, Apigenin, Rosameric acid, Octane, Nonane, Benzene, Iedol, Cadinene, Borneol
Seeds [11,12,18,19]	Fixed oil	Linoleic acid, Linolenic acid, Oleic acid, Palmitric acid, Stearic acid, Sitosterol, Dilinoleno-linolins, Linodilinolin, Hexoureic acid
Whole plant [20]	Secondary metabolites	Alkanoids, Steroids, Tannins, Phenol compounds, Flavonoids, Resins, Fatty acids, Gums

Pharmacological activity

Analgesic Activity

Fresh leaves of tulasi were investigated for analgesic activity using rat tail method. *Tulsi* showed an increase of 20.34 per cent with mild dose, 43.80 percent with moderate dose and of 51.47 percent with maximum dose at 90 min. after injection. The regression line indicated that the analgesic effect remain upto 3 hours irrespective of dose concentration. Analysis of variance revealed that the analgesic activity of Tulsi was statistically significant with all the three doses [p ≤ 0.01][21].

The analgesic activity of fixed oil from the seeds of *Ocimum sanctum* (OS) were investigated in mice and rats using the tail flick, tail clip, tail immersion and acetic acid-induced writhing methods. It was found it be effective against acetic acid induced writhing in dose dependent manner, suggesting that writhing inhibiting activity of the oil is peripherally mediated due to combined inhibitory effects of prostaglandins, histamine and acetylcholine[22].

Antiinflammatory Activity

The fresh tulsi leaf in its paste form was tested for anti-inflammatory activity using carrageenan induced paw edema model in comparison to Indomethacin. The percent inhibition of 500 mg/kg of the tulsi paste was found to be 88.15% as that of the response observed with 100 mg/kg of indomethacin and showed considerable anti-inflammatory activity[23].

Anti-inflammatory activity of essential oil extract of *Ocimum sanctum* L. leaf (Eugenol) was studied in wistar rats by using carrageenan induced hind paw edema method. The extract was administred 100 mg/kg body weight per i.p and the standard paracetamol was also administered 5 mg/kg body weight per i.p. The extracted Eugenol and paracetamol exhibited significant (p< 0.05%) activity when compare with carrageenan control[24].

Different extracts of stem, leaf and stem calli of OS were tested for antiinflammatory activity using carrageenaninduced rat paw oedema model in comparison with the standard indomethacin. The ethanol extract of callus tissue exhibited maximum significant anti-inflammatory activity out of all extracts studied followed by ethanol extracts of leaves of OS[25].

Ocimum sanctum fixed oil and linolenic acid were found to possess significant antiinflammatory activity against PGE2, leukotriene and arachidonic acid-induced paw edema. Plant lipids like linseed oil and soyabean oil containing linolenic acid when tested along with OS fixed oil, also showed

significant inhibition of carrageenan-induced paw edema. The results suggest that linolenic acid present in OS O fixed oil has the capacity to block both the cyclooxygenase and lipoxygenase pathways of arachidonate metabolism and could be responsible for the antiinflammatory activity of the oil[26].

Experimental studies of Tulsi have shown to inhibit acute as well as chronic inflammation in rats. This test was conducted by carrageenan induced paw edema, croton oil induced granuloma, and exudates at a dose of 500 mg/kg, bw/day. The oils processed from fresh leaves and seeds of *O. sanctum* have revealed anti-inflammatory effects on experimental animals induced by carrageenan, histamine, serotonin and prostaglandin E2 according to some studies. These experimental rats were administered with essential oil (200 mg/kg, bw) and fixed oil (0.1 ml/kg, bw) before injection of phlogistic agents and were compared with standard drug flurbiprofen. It was noted that Tulsi extracts could significantly reduce the edema whencompared with the saline treated control. However, its effect was less than the standard drug[27]. Fixed oil of Tulsi can prevent enhanced vascular permeability and leukocytic activity as evidenced by carrageenan induced inflammatory stimulus[28].

Antipyretic Activity

The antipyretic activity of fresh leaves of tulasi were evaluated by inducing fever using 15% of brewer's yeast suspension, injected subcutaneously in rats. 18 hrs after giving injection, each rat was fed orally with vehicle and test drug accordingly. Temperature was recorded to all animals at every 30, 60,120 and 180 minutes respectively. There was a significant reduction of fever in *Tulsi* group whereas the temperature control was not significant statistically in control group. Therefore the crude natural preparation of *Tulsi* itself, without any processing has effective antipyretic action[29].

The antipyretic activity of OS fixed oil was evaluated by testing it against typhoid paratyphoid A/B vaccine-induced pyrexia in rats. The oil on ip administration considerably reduced the febrile response indicating its antipyretic activity. At a dose of 3 ml/kg, the antipyretic activity of the oil was comparable to aspirin. Further, the fixed oil possessed prostaglandin inhibitory activity and the same could explain its antipyretic activity[30].

Antiulcer Activity

The aqueous extract of *Ocimum sanctum* (100mg /kg an 200 mg/kg orally) exhibited significant protection against ethanol induced gastric ulceration in Wistar rats. OS exhibits antiulcer activity by enhancing antioxidant potential of gastric mucosa there by reducing mucosal damage[31].

It was found that the ethanolic extract of OS not only reduced acid secretion, but also potentially elevated the mucoprotective effect and 100 mg/kg body weight was found to be the most effective dose in dose dependent manner indicating that OS extract exhibited antiulcerogenic in all the five models agaisnt ulcer induced by cold restraint (CRU), alcohol (AL), aspirin (ASP), and pyloric ligation (PL) model in rats, and histamine (HST) induced duodenal ulcer model in guinea pigs[32].

The fixed oil of OS administered i.p. shows significant antiulcer activity against aspirin, indomethacin, alcohol (ethanol 50%), histamine, reserpine, serotonin or stress-induced ulcers in rats. The fixed oil significantly possessed antiulcer activity due to its lipoxygenase inhibitory, histamine antagonistic and antisecretory effects[33].

Ashok Kumar *et al.,* (2011) while working for antiulcer activity of poly herbal formulation (PHF) containing *Ocimum sanctum*, *Abutilon Indicum* and*Triumfetta Rhomboidea* in indomethacin and Ethanol induced ulcers showed that PHF has potential antiulcer activity as comparable with standard drugs like Misoprostol (0.012mg/kg) and Omeprazole (10mg/kg), at a dose level of 200mg/kg.

Antiarthritic Activity

The fixed oil of *Ocimum sanctum* seeds was screened for antiarthritic activity by Singh et al. in 1996 using Freund's adjuvant arthritis, formaldehyde-induced arthritis and turpentine oilinduced joint edema in rats. The fixed oil showed significant anti-arthritic activity in both models and anti-edema activity against turpentine oil-induced joint edema[34].

Antiasthmatic Activity

50% aqueous ethanol extract of dried and fresh leaves, and the volatile and fixed oils of OS was evaluated against histamine and acetylcholine induced preconvulsive dyspnea (PCD) in guinea pigs. The 50% ethanol extract and volatile oil extracted from fresh leaves and fixed oil from the seeds significantly protected the guinea pigs against histamine and acetylcholine induced pre convulsive dyspnea. However, the 50% ethanol extract of dried leaves did not protect the guinea pigs against histamine induced preconvulsive dyspnea[27].

Antibacterial Activity

Biochemical compounds present in methanolic Tulsi leaf extract showing antimicrobial activity against human and fish pathogens were carried out using *Bacillus* sp*, E.coli, Streptococcus, Bacillus subtilis, Bacillus cereus, Staphylococcus aureus, Vibrio cholera, Salmonella typhi, Klebsiella pneumonia, Salmonella paratyphi and Fish pathogens Aeromonas hydrophila, Pseudomonas aeruginosa, Edwardsiella tarda.* Maximum antibacterial activity exhibited against *Bacillus* sp. and moderate activity in *Bacillus subtilis, Bacillus cereus, Vibrio cholera, Salmonella typhi.* Minimum activity was noted in *Salmonella paratyphi*. no inhibition zone was showed in *E.coli*., *Streptococcus sp, Staphylococcus aureus, Klebsiella pneumonia*. Whereas, the fish pathogens with methanolic crude extract of tulsi showed significant activity against *Aeromonas hydrophila, Pseudomonas aeruginosa* and *Edwardsiella tarda*[35].

Antimicrobial activity of different extracts (Ethanol, Methanol, Ethyl acetate and chloroform) of dried leaf of *O. sanctum* were tested against three human pathogens strains such as *Escherichia coli, Staphylococcus aureus* and *Candida albicans* through the well diffusion and the poison plate method. The Minimum inhibitory concentration (MIC) values of the crude extract of the tested plant leaves were determined. Both methods (well diffusion and poison plate) showed the strongest activity in methanol extract. Among four methanol extracts, they show more inhibition against in *S. aureus* than *E. coli* and *C. albican*.[36].

The antimicrobial activity of *Ocimum sanctum* leaf extract in normal tap water and local river water was investigated. The antimicrobial effect was studied with different concentration (100 to 600 mg l-1) of Tulsi leaf extract in tap and river water. In this, 600 mg l-1 concentration of plant extract treated water showed effective antimicrobial activity at 15 to 16 hrs than the other concentration of extract. The 500 mg l-1 of extract treated water showed 95 to 98% antibacterial activity in 14 to 16 hrs. The minimum bacterial concentration (MBC) was observed in 500 and 600 mg l-1 extract concentration. The concentration of the bacterial cells inhibited gradually for an hour was studied by spread plate method[37].

Antibacterial activity of the aqueous, alcoholic, chloroform extract and oil obtained from leaves of Ocimum sanctum were studied against *E.coli, P.aeruginosa, S. typhimurium* and *S.aureus*. Extract obtained from OS were observed equally effective against pathogenic gram positive and gram negative bacteria[38].

Tulsi is known to possess antimicrobial activity against various bacteria, the most common being *Candida albicans*, *Staphylococcus aureus*, *Escherichia coli* by its phytoconstituents isolated from various parts. In view of this, various studies have been conducted, wherein according to Singh *et al*., higher content of linoleic acid in *O. sanctum* L. fixed oil could contribute toward its antibacterial activity. The oil contains antibacterial activity against *S. aureus*, *Bacillus pumius*, and *Pseudomonas aeruginosa*, where *S. aureus* was the most sensitive organism[39]. Similarly Geeta *et al.* reported that on comparing alcoholic and aqueous extract, the aqueous extract of *O. sanctum* L. (60 mg/kg) showed wide zones of inhibition against *Klebsiella*[40].

Antimicrobial activity against pathogens like *Escherichia coli*, *Staphylococcus aureus*, *Bacillus anthracis*, *Bacillus subtilis*, *Salmonella* spp., *P. vulgaris*, *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis* were stuided and found its activity against *E. coli*, *Klebsiella aerogens*, *Proteus mirabilis*, *Salmonella typhimurium*, *Shigella dysentriae*, *Vibrio* spp., *P. aeruginosa*, cholera and *S. aureus*[41].

Antimicrobial activity was also found against *Pasturella multocida*, *E. coli*, *S. aureus*, *B. subtilis* and *Salmonella typhi*, *Salmonella paratyphi A* and *Salmonella typhimuriuum* and *E. coli*, *Klebsiella* spp., *B. subtilis*, *S. aureus* [42].

In vitro studies against specific pathogens suggest that essential oil of Tulsi leaves have significant inhibitory effect against *E. coli*, *B. subtilis*, *B. anthracis*, *S. aureus, Pseudomonas vulgaris* and *P. aeruginosa*. These essential oils include major constituents of leaves such as caryophyllene; eugenol, methyl eugenol which are effective against Arthobacterglobiformis, *B. megatherium*, *E. coli* and *Pseudomonas* sp[43].

Grover and Rao in 1977 stated that Eugenol is the most therapeutically effective constituent of Tulsi [44]. Aqueous and alcoholic extracts of leaves impart a potentially effective antibacterial activity. The extract is effective against various enteric pathogens viz., *E. coli*, *K. aerogens*, *P. mirabilis*, *Salmonella typhimurium*, *Shigella dysentriae*, *P. aeruginosa*, *Vibrio cholera* and *S. aureus*. Antibacterial activities of seeds were also studied and it was revealed that the crude, supernatant, residue and dialyzed samples obtained from the seeds inhibited the growth of *P. multocida*, *E. coli*, *B. subtilis* and *S. aureus*[45,46].

Growth inhibition of *Klesbiella*, *E. coli*, and Proteus and *S. aureus* by aqueous extract was studied. On the other hand, the aqueous extract has activity against the notorious multidrug-resistant strains of *S. aureus* which show resistance to beta lactam antibiotics. *O. sanctum* is also active against resistant strains of *Neisseria gonorrhea*, the fixed oil has an efficient good antibacterial activity against *Bacillus pumilus*, *P. aeruginosa* and *S. aureus*. Linoleic acid also has antibacterial activity. In addition to antibacterial the essential oil also has insecticidal properties. It has ten times the anti-tubercular potency of streptomycin and approximately one-fourth times the activity that of isoniazid. The essential oil is effective against pathogenic fungi including *Alternaria solani*, *Candida guillermondii*, *Colletotricum capsici*, *Curvularia* spp., *Fusarium solani*, *Helminthosporium oryzae* and the bacterial strains, *Anthrobacter globiformis*, *Bacillus megaterium*, *E. coli*, *Pseudomonas* spp., *S. aureus*, *S. albus* and *Vibrio cholerae* [47].

The essential oil has activity against both Gram-positive as well as Gram-negative bacteria. For enteric pathogens, aqueous extract and alcoholic extract is beneficial while on the contrary, seed oil of Tulsi yields considerable antimicrobial properties. The ethanolic extract inhibits methicillin-resistant *S. aureus* (MRSA) which is notorious for the production of B-lactamases and significant activity is also demonstrated against methicillin-sensitive *S. aureus* [MSSA]. The oils have antimicrobial activity against *Propioni bacterium* acnes. It has minimum inhibitory concentration (MIC) of 3.0% v/v. Viral encephalitis patients benefit from aqueous extract. Tulsi leaves paste was found effective against ring worm infections. Tulsi naturally possesses antimicrobial properties and is used in the treatment of many serious systemic diseases and localized infection. With fresh juice and honey, worms and parasites are removed; the sweetness excites the parasites out. It is used in the treatment of viral encephalitis, malaria and typhoid[48].

Tulsi demonstrated effective antimicrobial property against *Aggregatibacter actinomycetemcomitans*, suggesting its possible use as an effective and affordable “adjunct” along with the standard care in the management of periodontal conditions[49-52].

Antifungal Activity

Methyl chavicol and linalool obtained from essential oil of Ocimum sanctum showed significant antifungal activity against Candida, including azole-resistant strains. Their fungicidal action resulted from extensive lesions of the plasma membrane and a considerable reduction in the amount of ergosterol[53].

Antifungal activity of Ocimum sanctum leaves was determined against clinically isolated dermatophytes. Minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) of various extracts and fractions of OS leaves were also determined against dermatophytic fungi used[54].

Antiviral Activity

Different types of extracts of *Ocimum sanctum* have anti-viral activity against different viruses e.g. Hematopoietic Necrosis Virus (IHNV)[55], polio virus type 3[56], herpes virus (HSV), hepatitis B virus, New castle Disease Virus. Ethanolic extract of Tulsi plant leaves in a range of 22.5 mg/ml concentration inhibit replication of polio type 3 virus in VERO cells. The extracted components of this plant like linalool, apigenin and ursolic acid show broad spectrum antiviral activity against DNA viruses like RNA virus and adenoviruses[57,58]. One study also proves its efficacy against new castle disease of poultry [59].

Tulasi is used in most of the countries worldwide to help protect against swine flu. The main chemical constituents isolated from leaves are Ursolic acid, apigenin and luteolin. Several formulations are available in the market[60,61]. Boiled tulsi that is basil leaves served in a warm drink like tea can help prevent an outbreak of dengue. This bitter and pungent herb has all the properties that strengthen the internal system against fever[62].

Anti-helminthic Activity

The essential oil of Ocimum sanctum and eugenol, tested in vitro, showed potent anthelmintic activity in the Caenorhabditis elegans model[63].

Antiplasmodial Activity

Leaf extract, root extracts, the stem and flower extracts of OS showed excellent antiplasmodial activity in a study carried out by Inbaneson et all in 2012 on three different species of ocimum. The in vitro antiplasmodial activity might be due to the presence of alkaloids, glycosides, flavonoids, phenols, saponins, triterpenoids, proteins, resins, steroids and tannins in the ethanolic extracts of tested plants[64].

Larvicidal Activity

Larvicidal activity of essential oils and different extracts of Ocimum. Sanctum, O. basilicum and O. gratissimum were compared on laboratory reared and field collected larvae of

Culex quinquefasciatus. The LD50 value of O. basilicum and O. sanctum oil were 39.31 and 40.02 on laboratory reared larvae and 129.53 and 139.49 on field collected larvae. Laboratory reared larvae were more sensitive than field collected larvae.45 The acetone, chloroform, ethyl acetate, hexane, and methanol leaf and flower extracts of Ocimum sanctum were studied against fourth instar larvae of Aedes aegypti and Culex quinquefasciatus. The highest larval mortality was found in leaf extract of O. sanctum against the larvae of aegypti and C. quinquefasciatus[65].

Antioxidant Activity

The antioxidant effects of *Ocimum sanctum* were investigated in experimental streptozocin-induced diabetic rats. Administration of OS to streptozocin-induced diabetic rats for 30 days significantly reduced the plasma level of thiobarbituric acid reacting substances and improved the status of the antioxidant enzymes catalase, superoxide dismutase and glutathione peroxidase in vital organs such as the liver and kidney[66].

A hydroalcoholic extract of OS leaves has been investigated for its antioxidant activity in animal models of peptic ulcer with the aim of exploring a possible correlation between its antioxidant and antiulcer activities. The antioxidant activity was by evaluated by estimating plasma malondialdehyde (MDA) in ethanol treated rats and histamine treated guinea pigs and estimating superoxide dismutase (SOD) in pyloric ligated rats and histamine treated guinea pigs. In ethanol treated rats and histamine treated guinea pig ocimum sanctum leaf extract (100 mg/kg & 200 mg/kg) significantly decreased the levels of MDA in comparison the diseased control. The extract (100 mg/kg & 200 mg/ kg) also increased the levels of SOD in pyloric ligated rats and histamine treated guinea pigs when compared to the diseased control[67].

Antistress Activity

Fresh leaves of Ocimum sanctum were evaluated for antistress activity against experimentally induced oxidative stress in albino rabbits[68].

Anticancer Activity

Tulsi has been shown to possess an excellent anticancer activity[69]. Detoxification of carcinogens and mutagens which is carried out by enzymes such as glutathione-*S*-transferase, cytochrome b5 and cytochrome P450, and aryl hydrocarbon hydroxylase is modulated by the alcoholic extract (AlE) of leaves of *O. sanctum.* The anticancer activity of Tulsi has been reported against human fibrosarcoma cells culture, wherein AlE of the drug induced cytotoxicity at 50 mg/ml and above. In such studies, microscopically, the cells showed shrunken cytoplasm and condensed nuclei. The DNA was found to be fragmented when observed in agarose gel electrophoresis[70].

Antimelanoma activity of 50% alcoholic aqueous leaf extract of different species of Ocimum were investigated. Leaf extract administered orally (200mg/kg, p.o.) resulted in significant reduction in tumor volume, increase in average body weight, and survival rate of mice[71].

The seed oil of *Ocimum sanctum* was evaluated for anticancer activity against subcutaneously injected 20-methylcholanthrene induced-fibrosarcoma tumors in the thigh region of Swiss albino mice. The enhanced survival rate and delay in tumor incidence was observed in seed oil supplemented mice. Potential chemopreventive activity of the oil is partly attributable to its antioxidant properties. The chemopreventive efficacy of 100 microl/kg seed oil was comparable to that of 80 mg/kg of vitamin E[72].

Papilloma genesis induced by 7,12-dimethylbenz(a) anthracene (DMBA) significantly reduced the tumor occurrence in mice on topical application of *O. sanctum* leaf extract. The application of Tulsi extracts in the form of paste has shown promising results in the prevention of DMBA induced buccal pouch carcinogens[73].

Different types of carcinogens have been tried for evaluating the anticarcinogenic properties in the experimental animals induced by Tulsi leaves when fed to experimental rats with 600 mg/g diet for 10 weeks, significantly reduced the 3,4-benzo (a) pyrene [B (a) P] and 3'-methyl-4- dimethylaminoazobenzene (3'MeDAB)- induced squamous cell carcinoma and hematoma incidences[74].

Administration of 70% ethanolic Tulsi leaf extract has also been observed to reduce the incidence of cancer caused by *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG), a nitroso compound widely used as an experimental gastric carcinogen. MNNG is a potent mutagen and induces erosions of the gastric mucosa, an initial precancerous change integral for the initiation of stomach carcinogenesis. Intragastric administration of MNNG induces increased cell proliferation and angiogenesis with evasion of apoptosis leading to well differentiated squamous cell carcinomas. Administration of Tulsi has been

shown to decrease these activities wherein Tulsi extract influences the critical molecules involved in cell proliferation, invasion, angiogenesis, and apoptosis. A significant decrease in the levels of cytokeratin, CK (infiltration), vascular endothelial growth factor, VEGF (angiogenesis), proliferating cell nuclear antigen (PCNA), glutathione-*S*-transferase pi (key proteins involved in proliferation), and antiapoptotic protein Bcl-2 with simultaneous increase in the proapoptotic proteins Bax, cytochrome *c*, and caspase 3 were reported[75]. Studies also suggest that the leaf extract blocks or suppresses the biochemical events associated with chemical carcinogenesis by preventing metabolic activation of the procarcinogen to carcinogen. Previous studies suggested that AlE of Tulsi leaf before administering 7,12 dimethylbenz[*a*] anthracene causes decreased phase I enzymes; reduction in the levels of lipid and protein oxidation, and a concomitant enhancement of the antioxidant and phase II enzyme activities in the liver. Tulsi also causes a decrease in the 7,12-dimethylbenz[*a*] anthracene induced genotoxicity, as evaluated by the micronuclei formation in bone marrow cells in mice. These results suggest that, in association with the modulation of the phase I and II detoxification enzymes, Tulsi possesses antigenotoxic effects, and all these might have contributed to the reduction of chemical carcinogenesis[76].

Tulsi decreased the expression of cutaneous γ-glutamyl transpeptidase (GGT), a marker of tumor progression, and glutathione-*S*-transferase-P, which is increased in chemically induced hepatic tumors. The heat shock protein, which is altered during carcinogenesis, has also shown a decrease in its concentration[77].

Application of Tulsi extract decreased the activity of ornithine decarboxylase, an enzyme involved in the regulation of cell proliferation and development of cancer. There was also a concomitant decrease in the phase I enzymes and lipid peroxidation suggesting that *O. sanctum* prevents the activity of carcinogen induced cytochrome P-450 dependent enzymes and that this leads to a decrease in the formation of ultimate carcinogenic moiety[78].

Anticataleptic Activity

The anticataleptic activity of the aqueous extract (300 mg/kg, i.p) and the alcoholic extract (300 mg/kg, i.p) of the leaves of *Ocimum sanctum* was studied and observed a significant ($P < 0.001$) reduction in cataleptic scores[79].

Anticataract Activity

The Aqueous Extract of fresh leaves of OS (1g/kg and 2 g/kg) significantly delayed the the onset as well as subsequent maturation of cataract in galactosemic cataract model in rats by 30% galactose and naphthalene cataract model in rabbits by 1 g/kg naphthalene[80].

Wound healing

Wound healing activity of *Ocimum sanctum* is also proved by using two different types of concentration (200 and 400 mg/kg) in rats. The models of wound used for this study are: the excise, the incise and dead space wound model. By using Van Gieson and Masson Trichome strains in histological examination of determination of granuloma tissue, it is found that Ascorbic acid, Hexose amine, L-Hydroxyproline and Malondialdehyde isolated from Tulsi has wound healing activity. Tulsi can be used as adjunct therapies for the burn wound management many studies supporting its use in healing[81-83].

Anticoagulant Activity

Ocimum sanctum fixed oil (3 ml/kg, ip) was studied for anticoagulant activity. It was observed that blood clotting time was prolonged and the response was comparable to that obtained with aspirin (100 mg/kg). The effect appears to be due to the anti-aggregatory action of oil on platelets[84].

Antianxiety and Antidepressant Activity

The effect of ethanol extract of leaves of *Ocimum sanctum* in Swiss albino mice, against both anxiety and depressive disorders were investigated. Depression was studied through tail suspension test and forced swim test. Anxiety experiments included light dark test, elevated plus maze test, and holeboard test. The *Ocimum sanctum* extracts shows antianxiety and antidepressant properties at the same dose and can be a potential therapeutic agent against mixed anxiety and depressive syndrome[85].

Anticonvulsant Activity

Different extractives of stem, leaf and stem callus of *Ocimum sanctum* were tested for anticonvulsant activity against standard drug phenytoin using maximal electroshock (MES) model. Ethanol and chloroform extractives of stem, leaf and stem calli were effective in preventing tonic convulsions induced by transcorneal electroshock[86].

Antidiabetic Activity

Ten fractions (F1-F10) were isolated from hydroalcoholic extract of OS aerial part by

column chromatography. All the fractions F1 to F10 were screened for antidiabetic activity in alloxan induced diabetic rats by estimating serum glucose level and lipid parameters. The bioactive fraction (F5) was found to be potent antidiabetic by ameliorating glucose and lipid parameters (total cholesterol, triglycerides, low and high density lipoprotein cholesterol). The extensive spectroscopic data analysis reveals that, the isolated bioactive compound elucidated as tetracyclic triterpenoid[87].

The effect of ethanolic extract and five partition fractions of OS leaves on insulin secretion together with an evaluation of their mechanisms of action were studied and concluded that *Ocimum sanctum* leaf extracts stimulate insulin secretion from perfused pancreas, isolated islets and clonal pancreatic–cells[88].

The antidiabetic effects of Ethyl acetate, Petroleum-ether, and Chloroform fractions from ethanolic extract of the leaves of OS were investigated in normal and alloxan induced diabetic rats (AIDRs). Administration of these fractions to the AIDRs resulted in the significant elevation of liver glycogen content. In diabetic rats, SGOT and SGPT levels were significantly elevated that were further reduced after i.p. administration of these fractions. These results indicate that different fractions of OS have favorable effects in bringing down the severity of diabetes together with hepatoprotectivity[89].

Methanolic extracts of leaves of various Ocimum species were explored and compared for antidiabetic activity. All extracts were able to show antidiabetic activity at 0.5 mg/Kg concentration. The activities are well comparable with the standard drug, glibenclamide. The methanolic extract of OS showed better antidiabetic activity in comparison with other species of Ocimum and standard drug. The data were verified as statistically significant by using one way ANOVA at 5 % level of significance ($p < 0.05$)[90].

Antifertility activity

Treatment of albino rats with a benzene extract of *Ocimum sanctum* leaves (250 mg/kg body weight) for 48 days decreased total sperm count, sperm motility, and forward velocity. The results suggest that such effects are due to androgen deprivation, caused by the anti-androgenic property of OS leaves. The effect was reversible because all parameters returned to normal 2 week after the withdrawal of treatment.24 A significant decrease was noted in the sperm count in rabbits. Serum testosterone levels showed marked increase while FSH and LH levels were significantly reduced in OS-treated rabbits (2 g fresh leaves/rabbit for 30 days). The results suggest the potential use of OS as an effective male contraceptive agent[91].

Antihyperlipidemic and Cardioprotective Activity

The antihyperlipidemic and cardioprotective activity of *Ocimum sanctum* fixed oil was studied in rats fed with a high fat (HF) diet and concluded that treatment with OS fixed oil decreased the high serum lipid profile and expressed antiartherogenic and cardioprotective actions against hyperlipidemia. The anti-hyperlipidemic action of OS fixed oil was mainly resulted from the suppression of liver lipid synthesis. Linolenic acid and linoleic acid contained in Ocimum sanctum fixed oil were possibly responsible for both lipid-lowering and cardiac protective action against hyperlipidemia[92].

In Streptozotocin induced diabetic rats, aqueous extract of tulsi was administered for eight weeks and decrease in lipid profile was observed[93].

Antihypertensive Activity

The OS fixed oil administered i.v. produced hypotensive effect in anaesthetized dog, which seems to be due to its peripheral vasodilatory action. Essential fatty acids like linoleic and linolenic acids, contained in the OS oil produce series 1 and 3 (PGE1 and PGE3) prostaglandins and inhibit the formation of series 2 prostglandins (PGE2)[84].

Antitussive Activity

Aqueous and methonolic extract of *Ocimum sanctum* was studied for antitussive activity in guinea pigs at the doses of 1.55 gms and 0.875 gms/kg body wt respectively. Cough was induced by exposure to the aerosol of citric acid (7.5% w/v). The study showed that both the test extracts posses significant antitussive activity and aqueous extract showed a higher activity than the methonolic extract[94].

Antiemetic Activity

Tulsi leaves also check vomiting and used for antiemetic action[95].

Antithyroidic Activity

Effects of *Ocimum sanctum* leaf extract was investigated on the changes in concentrations of serum T3, T4 in the male mouse. OS leaf showed anti-thyroidic activity[96].

Eye Disease

The leaf juice of *Ocimum sanctum* along with triphla is used in ayurvedic eye drop preparations recommended for glaucoma, chronic conjunctivitis & other painful eye disease. In daily routine one may use about three drops of tulsi oil alog with honey and it is supposed to improve eye sight[97].

Genoprotective Activity

Protective effect of *Ocimum sanctum* was evaluated on chlorpyrifos-induced genotoxicity in in vivo and in vitro models. It was observed that rats pretreated with OS extract, showed a significant (P<0.01) increase in mitotic index a significant decrease in the frequency of aberrant cells as compared to the rats treated with chlorpyrifos alone. A significant (P<0.05) increase in chromosomal aberrations was observed in cultures treated with 75 µg/ml chlorpyrifos as compared to controls, which decreased significantly (P<0.05) with Ocimum sanctum extract pretreatment[98].

Hepatoprotective Activity

The hepatoprotective activity of Ocimum sanctum alcoholic leaf extract was studied against paracetamol-induced liver damage in Albino rats synergism with silymarin and concluded that Ocimum sanctum alcoholic leaf extract showed significant hepatoprotective activity and synergism with silymarin[99].

When alcoholic extract of Tulsi plant orally administered, it exhibited hepatoprotective effect against Paracetamol, Carbon tetrachloride and anti-tuberculosis drugs induced liver injury in albino rats. When extract of *Ocimum sanctum* were used in male albino rats weighing 100-150 g of Wistar strain (5-6 weeks) the level of enzymes was reduced. Biometry Research Unit, Indian Statistical Institute, 203 revealed that cold water extract of Tulsi plant produced hepatotonic effect against Paracetamol and Carbon tetrachloride when albino rats fed orally for 6 days with Tulsi extract[100].

Diuretic activity

The diuretic activity of aqueous extract of *Ocimum sanctum* was investigated in healthy Wistar albino rats. The study was conducted in saline primed Wistar albino rats (n=6) using frusemide (20 mg/kg per oral) as the reference diuretic drug with two oral doses of ethanolic extract of *Ocimum sanctum* (L.) 250mg/kg and 500mg/kg respectively. Urine volume and electrolytes (Sodium, Potassium and Chloride) excretion was estimated at the end of 24 hours. Data was analyzed by ANOVA followed by Tukey's test. $P < 0.05$ was considered as statistically significant. Ocimum sanctum extract significantly increased the volume of urine (5.48±0.13ml/100g/24hr and 7.52±0.19ml/100gm/24hr), increasing the diuretic index to 1.65 and 2.26 for 250mgkg and 500mg/kg dose ranges respectively (P< 0.01). The test drug, when compared to the control group, showed a significant increase in the excretion of sodium, potassium and chloride excretion. There was an increase in the saluretic index as reflected by the Na/K ratio to 2.2 and 2 respectively for the two dosages studied when compared to frusemide which showed a saluretic index of 1.81. These findings support the use of *Ocimum sanctum* as a diuretic agent with an action similar to that of the loop diuretic, frusemide[101].

Immunomodulatory Activity

The aqueous extract of Ocimum sanctum at the oral doses of 100, 200 mg/kg/day in rats enhanced the production of RBC, WBC, haemoglobin and also enhanced the production of antibodies without affecting the biochemical parameters[102].

Modifications in the humoral immune response in rats was observed when treated with distilled extract of fresh leaves attributing to mechanisms like antibody production, tissue responses, release of mediators of hypersensitivity in specific organs. Seed oil was observed to regulate both cell mediated and humoral immune response. The GABA pathways may demonstrate the immunomodulatory effects. Tulsi enhances both cellular and humoral immunity[103].

The aqueous extract of leaf had immunotherapeutic potential in sub-clinical trials of bovine during intra-mammary aqueous extract infusion and it was also stated that *Ocimum sanctum* L. aqueous extract produces a reduction in the bacterial total count and an increase in the count of neutrophil and lymphocyte and demonstrated a good phagocytic ability[104].

The immunomodulatory effects produced by *O. sanctum* L. seed oil was studied in both non-stressed as well as stressed animals for some immunological parameters. Consequently, it was stated that Tulsi seed regulates both humoral and cell-mediated immune responses mediated by GABAergic pathway. Godhwaniet al. checked the immunoregulatory effect demonstrated by both methanolic extract along with an aqueous suspension of Tulsi leaves for the treatment of antigenic challenge provoked by *Salmonella typhosa* together with sheep erythrocytes and to quantify antibodies that had been agglutinating by Widal agglutination and sheep

erythrocyte agglutination tests and in albino rats. The results indicated an immune stimulation of humoral immunogenic response due to increased antibody titer in the Widal together with sheep erythrocyte agglutination tests[103,105,106].

Tulsi is an effective immunomodulatory plant. Modification in the humoral immune response was observed by distilled extract of fresh leaves. Aqueous extract of leaves *in vitro* showed that leaves had proliferative as well as inhibitory effect on splenocytes. In comparison to negative control, 42.17, 55.42 and 47.38% increasein the proliferation of spleen cells were reported when splenocytes culture was treated with 31.25, 62.5 and 125 µg/ml Hot aqueous extract of *O. sanctum* In comparison to positive control, spleen cells with Hot aqueous extract of *O. sanctum* leaves in presence of Con-A exhibited 1.25 and 12.36% increase in the proliferation of spleen cells when splenocytes culture was treated with 31.25 µg/ml and 62.5 µg/ml HAE of *O. sanctum*, respectively. The methanolic extract together with an aqueous suspension of *O. sanctum* leaves produced clinically evident immunostimulation of humoral immunological response[107].

A combination of *O. sanctum*, ascorbic acid and verapamil were given to experimental animals exposed to cocaine, they enhanced the macrophage function and decrease oxidative stress. Aqueous and ethanolic extract of leaves was used to study immunomodulatory activity on specific and nonspecific immunity in mice, that show strengthening of both specific and non-specific responses that can be assessed with haemagglutination antibody (HA) titer, neutrophil
adhesion test, Delayed Type Hypersensitivity (DTH)[106,108].

Neuroprotective Activity

Ocimum sanctum shows ameliorative potential in attenuating vincristineinduced peripheral neuropathic pain in rats, which may be attributed to decrease in oxidative stress and calcium levels. Administration of OS (100 and 200 mg/kg p.o.) and its saponin rich fraction (100 and 200 mg/kg p.o.) for 14 days significantly attenuated vincristine-induced neuropathic pain along with decrease in oxidative stress and calcium levels[109].

Memory Enhancer Activity

Aqueous (300 and 500 mg/kg) and alcoholic (300 and 500 mg/kg) extracts of *Ocimum sanctum* Linn. Leaves were studied for antidementic and anticholinesterase effect in rats. Maximal electroshock, atropine, and cyclosporine were used to induce dementia. The passive avoidance taskwas used for assessing memory. Acetylcholinesterase (AChE) activity was estimated in different parts of the brain, and immune status was studied using dinitrochlorobenzene (DNCB) skin sensitivity tests. In all the three models both aqueous and alcoholic OS extracts decreased the time taken to reach the shockfree zone and the number of mistakes and significantly decreased the AChE activity in rats. OS treatment significantly increased the induration in the DNCB skin test. Therefore, OS was shown to be useful for the management of experimentally induced cognitive dysfunctions in rats[110].

The alcoholic extract of dried whole plant of OS ameliorated the amnesic effect of scopolamine (0.4 mg/kg) and aging-induced memory deficits in mice. Passive avoidance paradigm served as the exteroceptive behavioural model. OS extract increased step-down latency (SDL) and acetylcholinesterase inhibition significantly[111].

Various behavioural tests and biochemical were performed to explore the possible role of OS in alzheimer's disease.OS exhibited anxiolytic activity in open field test. In elevated plus maze test OS significantly allevated ibotenic acid and colchicine induced anxiety and depression in Porsolt's swim test. In Morris' water maze test, OS pretreatment improves reference memory, working memory and spatial learning. Both ibotenic acid and colchicine induced deficits in active avoidance learning and retention of learned behavior were significantly reversed. OS might be effective in clinical Alzheimer's disease by virtue of its cognition enhancement, antidepressant and antianxiety properties, which are primary needs to be addressed in alzheimer's disease[112].

Radio-protective Activity

Joseph et al., in 2011 studied the radioprotective effect of *Ocimum sanctum* on the salivary gland of rats administered radioiodine ((131)I) and compared its efficacy with a known radioprotectant, amifostine. OS and amifostine presupplemented and subsequently exposed to (131)I rats at 3 and 6 months duration exhibited comparable histopathology with controls. The study indicated possible radioprotective effect of OS and amifostine against high-dose (131)I exposure[113].

Flavonoids extracted from the leaves of, OS were studied as a raddioprotector on the erythrocyte antioxidants in oral cancer. Results

of the study suggest that erythrocytes from cancer patients responded to oxidative stress by elevating glutathione levels, while a decrease in glutathione levels observed in OS flavonoids treated patients , could be due to the free radical scavenging effect of OS flavonoids, sparing the glutathione. However OS flavonoids did not seem to exert its effect on other antioxidants of erythrocytes[114].

Antidote activity

OS showed antidote activity to many poisons. OS can be used antidote for dog bite, scorpion bite, snake bite and insect bites[115-117].

Toxicity Studies

The median lethal dose (LD50) of OS fixed oil was determined after ip administration in mice. The fixed oil was well tolerated up to 30 ml/kg, while 100% mortality was recorded with a dose of 55 ml/kg. The LD50 of oil was 42.5 ml/kg. There was found no untoward effect on subacute toxicity study of OS fixed oil at a dose of 3 ml/ kg/day, ip for 14 days in rats[118].

Acute toxicity studies of leaves powder of ocimum plant material was carried out in swiss mice weighing 25-35 gms by administering a dose of 3, 5 & 7mg/kg body weight orally in the form of aqueous slurry. The groups were almost continuously observed for mortality and behavioral changes during first 24 hrs and then daily for a fortnight. The observations of changes in body weight, food and water intake as well as cage side observations were reported. There was no abnormality observed in any of these 3 groups. The whole plant powder was found to be nontoxic[119].

The present study was aimed to study the acute and subacute toxicity studies with orally administered 50% ethanolic leaves extract of Ocimum sanctum Linn (OSE). In acute toxicity tests, four groups of mice (n = 6/group/sex) were orally treated with doses of 200, 600, and 2000 mg/kg, and general behavior, adverse effects, and mortality were recorded for up to 14 days. In subacute toxicity study, rats received OSE by gavage at the doses of 200, 400, and 800 mg/kg/day (n = 6/group/sex) for 28 days, and biochemical, hematological, and histopathological changes in tissues (liver, kidney, spleen, heart, and testis/ovary) were determined. OSE did not produce any hazardous symptoms or death and CNS and ANS toxicities in the acute toxicity test. Subacute treatment with OSE did not show any change in body weight, food and water consumption, and hematological and biochemical profiles. In addition, no change was observed both in macroscopic and microscopic aspects of vital organs in rats. Our result showed that Ocimum sanctum extract could be safe for human use[120].

On administration by oral route, approximate LD50 of *Ocimum sanctum* was found to be 4505±80 mg/kg body weight(bw) and by intra-peritoneal (ip) routes, 3241±71 mg/kg, bw. OS leaves aqueous and alcoholic extracts with graded doses (3500–6300 mg/kg, bw) were injected ip in mice, and after a period of 72 hours it was observed that aqueous extract administration at doses up to 5 g/kg body weight did not produce any toxic effect ie 100% safe while 80% tolerance was shown by alcoholic extract up to a dose of 4g/kg, bw. The acute LD50 (30) values for aqueous extract was found to be 6200 mg/ kg, bw while that of alcoholic extract was found to be 4600 mg/kg, bw[121].

CONCLUSION

It is evident that Tulsi is a medicinal plant of great importance because of its varied application in medicine, and hence can be corroboratively called the “Queen of Herbs.” . Several medicinal properties have been attributed to the plant not only in Ayurveda and Siddha but also in Greek, Roman and Unani. The vast survey of literature showed that *Ocimum sanctum* has a huge spectrum of pharmacological activities. Several research offers evidence that Tulsi is useful against stress; it enhances stamina and increases efficient use of oxygen by body; strengthens immune system; reduces inflammation; protects from radiation; reduces aging; supports the lungs, liver and heart; it exhibits antibiotic, antiviral and antifungal, antioxidant properties. Different parts of plant have been used in Ayurvedic ancient Medicine to cure an array of ailments including common cold, cough, headache, flu, asthma, fever, colic pain, sore throat, bronchitis, hepatic diseases, malaria fever, flatulence headaches, fatigue, skin diseases, wound, insomnia, arthritis, influenza, digestive disorders, night blindness, diarrhea. Tulsi acts as an adaptogen that helps the body and mind to encounter different physical, chemical emotional and infectious stresses, and restore physiological and psychological functions. So it can be concluded that *Ocimum sanctum* L. or tulsi is a traditionally and clinically proved medicinal herb for both its application and efficacy.

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