**INTRODUCTION**

The use of medicinal plants dates back not only to human civilization but to ancient living beings also. Plants have been crucial in sustaining human health and wellbeing of mankind. The word “drug” taken from French word “Drogue” which means “dry herb”, strongly suggests that earliest drugs were taken from plant sources. Earliest people used to treat diseases by unconventional methods using plants, animal products and minerals, of them plants were given major priority. Each and every secondary metabolite has unique pharmacological action, mechanism of action and therapeutic uses. So, plants or products isolated from them have been used to treat infections, health disorders or diseases from centuries ago till date. The current review article gives the importance and various pharmacological actions of five plants namely *Calendula officinalis, Tagetes erecta, Carica papaya, Hypericum perforatum and Salvia officinalis* which have certain activities in common based on the literature survey. All of them have been used in holistic system of medicine and many scientific experiments have been done to prove their activities. Most of them have good amount of flavonoids that make a suitable antioxidant, anti-inflammatory, hepatoprotective, cardioprotective and nephroprotective agents in general. Apart from them, they have other individual constituents responsible for their unique pharmacological activities. Combinations of such plants based on the activity needed can be formulated to a new synergistic formulation instead of extracting the individual constituent fractions from it. They are thus been studied extensively to get a safe and efficacious product.

**Keywords:** *Calendula officinalis, Carica papaya, Hypericum perforatum, Pharmacological action, Salvia officinalis, Tagetes erecta.*

**CALENDULA OFFICINALIS**

*Calendula officinalis* Linn. also called as pot marigold belongs to the family Compositae (Asteraceae). Its Indian native names are *Chamanthipooovu* (Telugu), *Sendigai* (Tamil), *Genda* (Hindi), *Gulsarfi* (Punjabi).3,4 The name of this plant comes from a Latin word ‘Calen’ meaning the first day of each month, because of the long flowering
period of plant. As flowers move in the direction of the sun’s radiation, it has become an astronomical sun sign “Leo” (Dinda and Craker, 1998).5 It is widely distributed in Southern Europe, Mediterranean region, North Africa, Asia and America. It is an annual or sometimes biennial plant with erect stems upto 40-70cm tall. It has a deep tap root. The leaves are alternate, petiolate, oblong, spatulate, margins, entire or with few hairs and hairy. The flowers are large heads, 5-7cm in diameter and blooms from June to early November. The flower is an inflorescence and each flower head is composed of many tiny flowers, yellow or orange, arranged in a chapter or floral disc. Each flower head is a receptacle or involucre where the flowers are arranged. It consists of bracts and rises on a long peduncle or flower stalk. Radiated flowers – in the middle of the floral heads yellow florets are arranged in the centre (male) and at the periphery, there are ray florets (female) that look like orange petals. Calendula fruit is thorny, curved achenes. They have no pappus. The entire plant has a strong unpleasant odour.5

VARIOUS PHARMACOLOGICAL ACTIONS OF CALENDULA OFFICINALIS

Wound Healing Activity

In an invitro study, it was found that the Calendula flower extract showed significant healing activity against thermal burns in rats by increasing hexosamine and collagen hydroxyproline content with a significant decrease in the level of tissue damage marker enzymes (aspartate transaminase and alkaline phosphatase) and acute phase proteins (orosomycid and heptaglobin). A decline in lipid peroxidation showed its antioxidant activity of Calendula.7,8

Periodical application of Calendula gel (2%) causes significant healing of wounds due to its antioxidant and antimicrobial activities.7,9

Calendula might facilitate the wound healing by increasing wound angiogenesis, epithelialization, and nucleoprotein, glycoprotein and collagen metabolism leading to improvement in local circulation and granulation tissue formation.7,10

The Calendula treatment was more effective than other medicines and also reduces discomfort during dressing changes. The use of 10% Calendula solution along with 2% Calendula gel for cleaning skin lesions, burn, and venous ulcers reduces the time of healing and also results in a greater number of healed wounds when compared to the use of Calendula solution alone.7,9

The topical application of Calendula in cream form leads to the healing of achilles tendon by increasing the collagen and non-collagen protein concentration as well as by organizing the collagen proteins.7,11

Immuno-stimulant Activity

Calendula officinalis polysaccharide fraction exhibits immuno-stimulant activity. Polysaccharide-I and Polysaccharide-II exhibited 40 to 57% and 20 to 30% of phagocytosis, respectively, while Polysaccharide-III exhibited the highest (54 to 100%) phagocytosis.12,13

Spasmodogenic and Spasmolytic Activity

The aqueous/ethanolic plant extract has shown spasmodogenic activity. The aqueous/ethanolic extract of Calendula flowers caused relaxation of spontaneous contraction and K+ induced contraction of muscles. The fractionated extract with dichloromethane inhibited spontaneous contraction. Calcium channel blockade (CCB) was responsible for spasmodlytic activity and thus can be understood while considering the main physiology.14

Hepatoprotective Activity

Calendula flower hydro-alcoholic extract caused 28.5% reduction in lysis of hepatocytes of CCl₄-intoxicated rat liver due to reduction in glutamo-pyruvate transaminase and glutamo-oxalate-transaminase.7,15 Moreover, CCl₄ intoxicated rats pre-treated with Calendula floral extract could protect against CCl₄ induced toxicity and showed an improvement in function of liver due to significant anti-oxidant activity and free radical scavenging activity of bioactive metabolites that includes flavonoids and terpenoids of Calendula.16

Anti-Inflammatory and Anti-Oedematous Activity

Calenduloside B (trioside of oleinic acid) of Calendula roots show sedative and anti-phlogistic activity.17

Calendula officinalis inflorescence extract shows anti-inflammatory activity against the dextran and carrageenan-induced acute paw oedema in mice.7,18

Anti-Bacterial and Antifungal Activity

Calendula has various anti-bacterial and anti-fungal activities.19

Calendula officinalis flower extract has an antibacterial activity against various bacteria. In-vitro, the essential oil of flowers inhibited the growth of gram-positive bacteria like Staphylococcus aureus, Bacillus subtilis and gram-negative bacteria like Pseudomonas aeruginosa, Escherichia coli, showing maximum inhibition of Pseudomonas aeruginosa. The petals showed more activity compared to the reproductive parts of the plant.7,19

The flower’s volatile oil showed anti-fungal activity against various fungal strains namely Candida dubliniensis (ATCC777), Candida krusei (ATCC6528), Candida glabrata (ATCC90030), Candida albicans (ATCC64548), Candida parapsilosis (ATCC22019) and against yeast isolated from humans: Candida krusei, Candida dubliniensis, Candida guilliermondii, Candida glabrata, Candida albicans, Candida parapsilosis, Candida tropicalis and Rhodotorrella spp.20

Glycosides of oleanolic acid and saponins of Calendula officinalis showed anti-parasitic activity against Heligmosomoidespolygyrus.21 Nerolidel of C. officinalis
showed anti-malarial activity by inhibiting the parasite to synthesize coenzyme Q in all intraerythrocytic stages.\textsuperscript{7,22}

**Anti-HIV Activity**

Calendula flower tincture showed antiviral activity by suppressing the replication of influenza APR-8, influenza A2 and herpes simplex virus.\textsuperscript{7}

**Anti-Cancer Activity**

The ethyl acetate soluble fraction of Calendula flower extract showed cytotoxic effect due to the presence of two main compounds: calenduloside G’6-O-methyl-ester and calenduloside F’6-O-butyl-ester (in vitro).\textsuperscript{23} Both showed anti-cancerous activity against melanoma (UAAC-62, SK-MEL-5 and LOXIMVI), leukemia (RPMI-8226 and MOLT-4) and colon cancer (HCC-2998) cell lines.\textsuperscript{24}

Thirteen saponins isolated and identified from *Calendula officinalis*, *Calendula arvensis* and *Hedera helix* showed mutagenic and antimutagenic activities using a modified liquid incubation technique of the Salmonella/microsomal assay. The Salmonella tester strain TA98±S9 mix was used. Screening of the antimutagenic activity was performed with a known promutagen: benzo-[a]pyrene and mutagenic urine concentrate from a smoker. Antimutagenic activities were also compared with the activity of chlorophyllin. All the saponins were found to be non-toxic and non-mutagenic for dose of 400ug/kg.\textsuperscript{7}

**Antidiabetic and Anti-Hyperlipidaemic Activity**

Alloxan (150mg/kg) of body weight was given to the rats by single intraperitoneal injection to induce diabetes. The blood glucose level and urine sugar level were significantly elevated in diabetic rats when compared to normal rats. Upon oral administration of hydro alcoholic extract of *Calendula officinalis* in diabetic rats at dose 25 and 50mg/kg body weight significantly lowered the blood glucose and urine sugar compared to diabetics rats. 100mg/kg body weight of hydroalcoholic extract of *Calendula officinalis* was found to be significant as it restored all the parameters to the normal levels of blood glucose, urine sugar and serum lipid in alloxan diabetic rats. The extract increases the total haemoglobin level. The extract was similar to that of insulin. Thus, the investigation clearly shows that hydro alcoholic extract of *Calendula officinalis* has both antidiabetic and anti hyperlipidemic effects.\textsuperscript{7}

**Tagetes erecta**

Linn. also called as Mexican marigold or Aztec marigold belongs to the family Asteraceae. Its Indian native names are *Sthulupushpa* (Sanskrit), *Genda*, *Hajara*, *Hajri*, *Jhandu* (Hindi), *Shraovanashya avanthige* (Kannada), *Thulukkacevanti* (Tamil), *Banthi* (Telugu), *Tangla* (Punjabi).\textsuperscript{4,25} It is a herbaceous annual or perennial whose height ranges from 30–110 cm. The root is cylindrical, pivoting, with a fibrous and shallow branching system. The stem is striated, sometimes ridge, smooth or slightly with villi, cylindrical, oval and herbaceous to slightly woody, with aromatic resin channels in the bark, when squeezed. Opposite leaves at the bottom alternate at the top, up to 20 cm long, pinnate, composed of 11 to 17 leaflets, lanceolate to linear-lanceolate, acute to acuminate, serrated to sub-holders, the lower ones of each leaf frequently setiform (in the form of threads), the superiors are sometimes completely setiform; with abundant round glands.

Flowers are grouped in small heads or in solitary inflorescences, on peduncles they are ligulate with yellow colors to red. In the flowers of the disc: 150 to 250 in the simple heads, in the doubles it shows different degrees of transformation in ligules, yellow to orange corollas, of 8 to 10 mm in length. The fruits and seeds are: linear achenes 7 to 10 mm long, smooth or slightly covered with stiff hairs at the corners. It reproduces easily by seeds.\textsuperscript{26}

**VARIOUS PHARMACOLOGICAL ACTIONS OF TAGETES ERECTA**

**Anti-Oxidant Activity**

A research activity reported the antioxidant studies on the ethanolic extract of *Tagetes erecta* flowers by three different assays like DPPH, reducing power and super oxide radical scavenging activity at different concentrations. In all the three assay, *Tagetes erecta* showed better reducing power than the standard (ascorbic acid). The super oxide anion scavenging activity and DPPH antioxidant activity was comparatively less than the standard. However, ethanolic extract of *Tagetes erecta* showed antioxidant property in all the in vitro models.\textsuperscript{27,28}

**Antimicrobial Activity**

The anti-bacterial activity of different solvents of *Tagetes erecta* flowers against Alcaligenes faecalis, Bacillus cereus, Campylobacter coli, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Streptococcus mutans* and *Streptococcus pyogenes* were reported. The flavonoid possesses anti-bacterial activity against all the tested strains and shows maximum zone of inhibition for *Klebsiella pneumoniae* (29.50 mm). The flavonoid Patuletin present in glycosidic form Patulitrin as well is one of the potential elements for its antibacterial activity.\textsuperscript{27,29}

An objective of a study was to investigate the antibacterial activity of this common locally available plant. Antibacterial activity of different part of ethanolic extract of *Tagetes erecta* was evaluated using disc diffusion
method against gram positive and gram negative bacterial strains. Streptomycin was the standard used for this work. The aim of this was to evaluate the antibacterial activity of extract from this plant part against five bacteria by using Disc Diffusion Method. The result indicated that the leaf and flower of this plant part showed a broad spectrum of antibacterial activity. 

The anti-microbial activity in 19 plants used in Colombian traditional medicine for cutaneous infections were screened against Neisseria gonorrhoeae (NG) by disc susceptibility assay. In all, 71% of the crude extracts exhibited antibacterial activity against the antibiotic susceptible NG strain, whereas 10% of the extracts inhibited penicillinase-producing NG strain GC1–182. It was reported that the Tagetes erecta flower parts showed maximum inhibitory action against NG strain. 

**Hepatoprotective Activity**

A research activity was reported regarding the hepatoprotective activity in flowers of Tagetes erecta by carbon tetra chloride induced hepatopathy model. The ethanolic extract showed the increase in serum ALT, AST, ALP and bilirubin levels. Ethyl acetate fraction of Tagetes erecta (EATE) at the dose of 400 mg/kg orally significantly decreased the elevated serum marker enzymes and level of bilirubin almost to the normal level compared to CCl4-intoxicated group. Phytoconstituents such as flavonoids, terpenoids and steroids are responsible for the observed hepatoprotective activity.

**Insecticidal and Mosquitocidal Activity**

Nikkon et al reported the insecticidal activity in flowers of Tagetes erecta by carbon tetra chloride induced stored product insect pest, Tribolium castaneum. The chloroform fraction showed highest toxicity against both the larvae and adults of Tribolium castaneum followed by petroleum ether fraction and ethanol extract. Thus they concluded that the flower of Tagetes erecta might be a pesticide against Tribolium castaneum.

Nikkon et al reported the mosquitocidal activity in ethanolic, chloroform and petroleum ether extracts of Tageteserecta flowers against different instars of Culex quinquefasciatus. Among the tested samples the chloroform soluble fractions showed the highest toxicity and consequently the LC50 values (14.14µg/mL, 17.06µg/mL, 36.88µg/mL and 75.48µg/mL) for all instar larvae of Culex quinquefasciatus. The larvae showed comparative tolerance in the course of increasing age and time. From this they concluded the flowers of Tagetes Verecta having good mosquitocidal activity.

**Nematocidal Activity**

A work was reported about the nematocidal efficacy of four medicinal plants viz. Azadirachta indica, Calotropis procera, Datura stramonium and Tagetes erecta was ascertained for the control of M. incognita. All leaf amendments at different dosages significantly improved the plant growth characteristics of okra and reduced root knot infections compared with the untreated control.

**Wound Healing Activity**

A research article was reported on the wound healing activity of carbopol gel prepared from hydro alcoholic extracts of Gymnema sylvestre and Tagetes erecta in excision wound model and burn wound models in albino mice. In excision and burn wound models, the Gymnema and Tagetes treated animals showed significant reduction in period of epithelization and wound contraction. The combined gel showed accelerated wound healing activity that can be attributed to synergism. The enhanced wound healing activity of hydro alcoholic extracts may be due to free radical scavenging action and the phyto constituents present in it which either due to their individual or additive effect fastens the process of wound healing.

**Anti-Oxidant and Analgesic Activity**

Bashir and Gilani reported the in vitro anti-oxidant and in vivo analgesic activities (acetic-acid induced abdominal writhing) on flower extracts of Tagetes erecta. The results showed the presence of a good antioxidant potential on dose-dependent (100 and 300 mg/kg) and analgesic effect also. The antioxidant and analgesic activities obtained seem to be in good accordance with the medicinal uses of Aztec marigold as an anti-inflammatory and analgesic.

Larvicidal activity was reported on the essential oil from Tagetes erecta against 3rd instars of Aedes aegypti and to determine the amounts of larvicidal thiophenes in all plant tissues. The oil obtained by steam distillation and analyzed by gas chromatography/mass spectrometry showed 14 compounds. The main compounds were found to be piperitone (45.72%), d-limonene (9.67%), and piperitenone (5.89%). This was active against larvae of Aedes aegypti, with LC50 of 79.78 µg/ml and LC90 of 100.84µg/ml. The larvicidal thiophene contents were higher in the roots and flowers as demonstrated by high-performance liquid chromatography analysis.

**CARICA PAPAYA**

![Carica papaya plant](Figure 3: Carica papaya plant)
Carica papaya

Linn. also called as Papaya belongs to the family Caricaceae. Its Indian native names are Pappalam (Samskrit), Poppayi, Pappoli (Tamil), Bappaayi (Telugu), Kappalam, Pappayam (Malayalam), Pappangaye, Peragi (Kannada), Popaiyah, Papeetha (Hindi). It is an erect, fast-growing, usually unbranched tree or shrub, 7-8 m tall, with copious latex, leaves clustered near top of plant, alternate, long-petiolate, blade suborbicular, palmately 7-11-lobed; lobes glabrous, toothed, flat; plants dioecious in nature, some monocious cultivars; flowers aromatic, male in drooping axillary panicles, with a 5-toothed green calyx and 5-toothed cream to yellow corolla; stamens 10; female flowers solitary or cymose in axils or below leaves, with 5 yellow nearly free petals to 5 cm long; ovary with 5 stigmas; fruit a large yellow to greenish-orange berry, oblong to nearly globose or pyriform, about 7.5 cm long and bitter in wild types, up to 45 cm long, with flesh 2.5-5 cm thick, sweet, juicy and of orange colour in cultivars; seeds numerous in central cavity, rounded, blackish, about 0.6 cm in diameter, each enclosed in a gelatinous membrane (arill).  

**VARIOUS PHARMACOLOGICAL ACTIONS OF CARICA PAPAYA**

**Antioxidants and Free Radical Scavenging Activity**

The leaves, seeds and juice of papaya shows free radical scavenging and antioxidants activity. The antioxidant activity of ethanol, petroleum ether, ethyl acetate, n-butanol and aqueous extract from seeds of *Caricapapaya* was evaluated. Ethyl acetate and n-butanol fractions demonstrated antioxidant and free radical scavenging activity than other fractions. Papaya juice is an efficient scavenger of highly reactive hydroxyl radicals, which decreased the lipid peroxidation levels and increased the antioxidant activity in rats.

**Anti-Inflammatory and Anti-Microbial Activity**

The aqueous leaf extract of papaya showed increase in protein content and also raised antibody production against ovalbumin. In addition, aqueous extract also showed decline in bacterial population and proliferation rate at higher doses as compared to control group. In contrast, aqueous extract showed anti-inflammatory and antimicrobial activities at higher doses.

Harrison Abia investigated the efficacy of treatments with *Carica papaya* is dependent on the quantity of the different chemical substances present in the preparation. The antibacterial and antifungal ability of both fresh and dried leaves of *Carica papaya* against bacteria and fungi of medical importance was carried out. The aqueous, ethanol and acetone extract of both the dried and fresh leaves were tested at 25, 50 and 100 mg/ml concentrations on both the bacteria and fungi isolates using the disc diffusion method. Results showed very significant broad spectrum antimicrobial activity against Gram-negative and Gram-positive bacteria and fungi. The organic extracts were more effective than aqueous extracts. The result further showed that the dry sample was effective against both Grampositive and Gram-negative bacteria while the fresh sample was more effective against Gram-negative bacteria. *Carica papaya* leaves showed a better antibacterial activity than antifungal activity.  

The latex of papaya and Fluconazole has synergistic action on the inhibition of Candida albicans growth. This synergistic effect results in partial cell wall degradation (as indicated by transmission electron microscopy observations).

**Dengue Fever and Platelet Count**

Aqueous extract of *Carica papaya* leaves administered to a patient affected with dengue fever twice daily for 5 consecutive days exhibited elevated platelet count from 55x10^3/ul to 168x10^3/ul. The juice prepared from *Carica papaya* leaves has shown significant increase of platelet count in randomized controlled trial conducted on patients with dengue fever and dengue haemorrhagic fever.

An investigation in the platelet increasing property of *Carica papaya* leaves juice in patients with dengue fever was done. An open labelled randomized controlled trial was carried out on 228 patients with DF and dengue haemorrhagic fever. Gene expression studies were conducted on the ALOX 12 and PTAFR genes. There was a significant increase in mean platelet count observed in the intervention group but not in the control group 40 hours since the first dose of *Carica papaya* leaves juice. Comparison of mean platelet count between intervention and control group showed that mean platelet count in intervention group was significantly higher than control group after 40 and 48 hours of admission. The ALOX 12 (FC=15.00) and PTAFR (FC=13.42) genes were highly expressed among those on the juice. It thus concluded that *Carica papaya* leaves juice significantly increase the platelet count in patients with dengue fever and dengue haemorrhagic fever.

**Antidiabetic Activity**

The ethanolic extract of *Carica papaya* leaves stated a significant reduction in blood glucose level and beta cells regeneration of pancreas in diabetic mice. Aqueous extract of unripe papaya fruit significantly inhibited the key enzymes α-amylase and α-glucosidase involved in type 2 diabetes and also inhibited the lipid peroxidation in rat pancreatic cells studied in vitro.

**Wound Healing Activity**

Aqueous extract of *Carica papaya* significantly enhance the wound healing that helps in treatment of wounds. Fruits and seeds of *Carica papaya* were evaluated for wound healing activity using wound excision model in diabetic rats showed significant reduction in the wound area compared to untreated diabetic control. It also showed increased granulation, elevated hydroxyproline content and deposition of collagen in the wound area.

Diabetic mice given fermented papaya preparation (FPP) showed effective recruitment of monocytes and...
proangiogenic response by the macrophages at the wound site resulting in wound closure.

**Antifertility Activity**

Papaya seed extract treated in male albino rats reduced the cauda epidymal and testicular sperm counts. Male Wistar rats treated orally with papaya seed extract (200mg/kg) showed hypertrophy of pituitary gonadotrophs and gradual degeneration of germ cells, sertoli cells and leydig cells of testis thereby drastically affects the male reproductive functions. The aqueous extract of papaya seed administered to male Sprague Dawley rats suppressed the steroidogenic enzymes in the testis and reversible changes happened when the extract was withdrawn after 30-45 days of treatment. Therefore, the papaya seed extract can be used as amale contraceptive.

**Nephroprotective Activity**

Maximum nephroprotection was offered by the extract at 400 mg/kg/day CPE which lasted up to 3 hours post-CCl4 exposure and these biochemical evidences were corroborated by improvements in the renal histological lesions induced by CCl4 intoxication. Studies showed that CPE has nephroprotective effect on CCl4 renal injured rats, an effect which should be mediated by the phyto components present in it via either antioxidant and/or free radical scavenging mechanisms. *Carica papaya* plant has the nephroprotective activity.

**HYPERICUM PERFORATUM**

**Figure 4: Hypericum Perforatum Plant**

*Hypericum perforatum* Linn. also called as perforated St. John’s Wort belongs to the family Hypericaceae. Its Indian native names are *Choli phulya* (Hindi), *Vettaipakku* (Tamil). It is native to Europe, Russia, Africa, Asia and introduced to North America from Europe. In India, it is found in Himachal Pradesh, Jammu and Kashmir, Uttar Pradesh, it typically grows from a woody, branched rootstock up to 1-3’ tall and features a showy display of star-shaped, yellow flowers (1 1/2” diameter) that bloom in pyramidal compound cymes in summer (June-August). Each flower has five yellow petals peppered with black dots, a pistil with 3 styles and a centre boss of bushy yellow stamens. Stem – clasping, elliptic to oblong leaves to (1 1/4” long) have translucent dots and black marginal punctations. Foliage has an unpleasant aroma when bruised or rubbed.

**VARIOUS PHARMACOLOGICAL ACTIONS OF HYPERICUM PERFORATUM**

**Anti-Bacterial and Anti-Viral Activity**

Antibacterial properties of *Hypericum perforatum* extracts were reported by Russian scientists in 1959. Hypericin inactivates enveloped viruses at different points in the viral life cycle. It was suggested that it can inactivate enveloped viruses by altering viral proteins, and not nucleic acids as targeted by antiviral nucleosides. Hypericin can also inhibit the ability of virus to fuse with cell membranes.

The main antibacterial component was determined to be hyperforin.

Methicillin-resistant and penicillin-resistant *Staphylococcus aureus* were especially susceptible to hyperforin. The MRSA strain was resistant to several types of penicillins, ofloxacin, clindamycin, erythromycin, cephalosporins, and gentamicin.

It was found that 3-hydroxy lauric acid in field-grown *Hypericum perforatum* has anti-HIV activity.

Regarding other viruses, an important finding is that hypericin completely inactivated bovine diarrhea virus in vitro in the presence of light.

**Anti-Inflammatory Activity**

A research work was done finding out the anti-inflammatory activity of Saint John’s Wort extracts and found that it inhibited the expression of proinflammatory genes like cyclooxygenase-2, interleukin 6, and inducible nitric oxide synthase (iNOS). Detailed experiments it was found that *Hypericum perforatum* extracts decreased the activity of januskinase 2, leading to a series of reactions that inhibited the down regulation of signal transducer and transcription (STAT)-1 α DNA binding, further disrupting gene transcription.

A research work found that pseudohypericin and hyperforin inhibited production of the inflammatory agent prostaglandin E2 (PGE2).

**Anti-oxidant and Neuroprotective Activity**

Recent research showed facts that extracts of *Hypericum perforatum* decreases oxidative stress and thus prevents neurotoxicity, inflammation, and gastrointestinal problems. Flavonoid rich extracts of *Hypericum perforatum* are effective against hydrogen peroxide induced apoptosis in PC12 cells (a cell line derived from the pheochromocytoma of the rat adrenal medulla). The standard extracts of *Hypericum perforatum* can prevent DNA fragmentation and shrinkage of cells as a result of the above activity. Thus, flavonoid extract of *Hypericum perforatum* may effectively treat oxidative stress-related
neurodegenerative disorders such as Parkinson’s and Alzheimer’s diseases.\textsuperscript{56}

A research work concluded that standardized extracts of *Hypericum perforatum* can be a treatment of choice for depressed elderly patients showing degenerative disorders associated with elevated oxidative stress.\textsuperscript{52}

**Anti – Depressant Activity**

Now a days getting depressed is on its rise and is leading to several unwanted activities. People of all age groups are prone to depression. Depression is thought to originate from a disruption of normal brain neurochemistry, specifically from a deficiency of amine neurotransmitters like acetylcholine, norepinephrine, dopamine, and serotonin (5-hydroxytryptamine [5-HT]). Anti-depressant drugs typically raise the levels of those neurotransmitters, especially in nerve-nerve synapses.\textsuperscript{57}

Early research suggested that hypericum is the main antidepressant constituent of Saint John’s Wort, stimulating capillary blood flow.

A study on rat brain mitochondria found hypericin to strongly inhibit the enzymes MAO-A and -B.\textsuperscript{58,59} MAO is involved in the degradation of amine neurotransmitters. Inhibiting their degradation boosts their levels in the synapse.

Hypericin showed a strong affinity for sigma receptors, which regulate dopamine levels, acts as a receptor antagonist at adenosine, benzodiazepine, GABA-A, GABA-B, and inositol triphosphate receptors, which regulate action potentials caused by neurotransmitters.\textsuperscript{60,61}

The recent research focuses on hyperforin as the anti-depression agent. Hyperforin is a potent reuptake inhibitor of serotonin, dopamine, noradrenaline, GABA, and L-glutamate from the synaptic cleft which shows another important constituent of Saint John’s wort having anti-depressant activity.\textsuperscript{52}

Blocking the reuptake of serotonin (5-HT) from the synaptic cleft alleviates symptoms of depression by allowing the serotonin to bind to 5-HT receptors and obtain a greater response.\textsuperscript{52}

Unlike synthetic antidepressants that block 5-HT receptors, hyperforin apparently inhibited serotonin uptake by elevating intracellular concentrations of sodium and calcium. This has shown the unique feature of Saint John’s wort – Hyperforin.\textsuperscript{62}

It was demonstrated that the influx of Na\textsuperscript{+} was mediated by non-selective cation channels. It was found that hyperforin acts on the subclass non-selective cation channels, increasing intracellular concentrations of both Na\textsuperscript{+} and Ca\textsuperscript{2+} ions. It was subsequently identified that the channel as being the transient receptor potential channel protein 6 (TRPC6). Thus, activation of TRPC6 by hyperforin led to an increase in sodium uptake by neurons, resulting in a decrease of the sodium gradient between the neuron and the synaptic cleft. The loss of the gradient decreases reuptake of the monoamine neurotransmitters. The mechanism by which hyperforin has been shown to act is therefore different from that used by conventional antidepressants, perhaps pointing the way to a new class of antidepressants.\textsuperscript{63}

Hyperforin also increases the number of 5-HT receptors, as shown by studies on rat brains, suggesting a possible long-term therapeutic benefit of SJW treatment.

Several clinical studies were also done for standardised hypericum extracts and there is consensus among the research studies published till date that shows the administration of *Hypericum perforatum* is clearly helpful for treating mild to moderate depression.\textsuperscript{52}

**Opium Dependence**

A research work was reported that *Hypericum perforatum* decreased the symptoms of opiate withdrawal in adult Wistar rats. The effectiveness of *Hypericum perforatum* was found to be equivalent to clonidine, an FDA-approved medication for treating withdrawal symptoms. Thus, it concluded that *Hypericum perforatum* may effectively treat opiate withdrawal symptoms in humans.\textsuperscript{52}

**Anti-Cancer Activity:**

Hyperforin inhibits tumour cell growth in vitro according to. The mechanism involved induction of apoptosis through the activation of caspases, which are cysteine proteases that trigger a cascade of proteolytic cleavage occurrences in mammalian cells. Hyperforin was also found to cause the release cytochrome C from isolated mitochondria. Schepmp et al concluded that hyperforin has a significant antitumor activity, abundantly available, has low toxicity in vivo and therefore can hold a field of interest in introducing it as a novel anti-cancer agent.

Hypericin was investigated as an anticancer agent as well, inhibiting the growth of cells derived from a variety of neoplastic tissues like glioma, neuroblastoma, adenoma, mesothelioma, melanoma, carcinoma, sarcoma, and leukaemia. The activity of hypericin is found to be due to its photodynamic properties. In the presence of light and oxygen, hypericin is a powerful natural photosensitizer and generates superoxide radicals that forms peroxide or hydroxyl radicals, or singlet oxygen molecules which can kill tumour cells thus proving it to be helpful in photodynamic therapy.\textsuperscript{52}

**SALVIA OFFICINALIS**

![Salvia officinalis plant](image)

**Figure 5: Salvia officinalis plant**

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Salvia officinalis Linn. also called as Common Sage belongs to the family Lamiaceae. Its Indian native names are Samudraphala, shati, vrdhadaru (Samskrit), Kamrkash, Samundarsok, Sathi (Hindi), Kachori (Kannada), Pulam-kizhanma (Malayalam), Chimaikkarpuram (Tamil), Kachorulu, kichili-baddalu (Telugu).\(^{64}\) It is widely distributed in many parts of the world – Spain along the Mediterranean coast, Dalmatian region of Yugoslavia, cultivated in Yugoslavia, Italy, Albania, Turkey, Portugal, Cyprus, England, Canada and USA. In India it is sparingly cultivated in Jammu. The plant is perennial plant about 2 ft height with a quadrangular, pubescent, branching, shrubby stem, furnished with opposite, petiolate, ovate-lanceolate, crenulate, wrinkled leaves of a greyish-green colour, sometimes tinged with red or purple. The flowers are blue, variegated with white and purple and or disposed on long terminal spikes in distant whorls, each composed of a few flowers and provided with ovate, acute, deciduous bracts. The calyx is tubular and striated with 2 lips, of which the upper has 3 acute teeth, the under 2. The corolla is tubular, bilabiate, ringent with the upper lip concave and the lower divided into three rounded lobes, of which the middle is the largest. The filaments are supported upon short pedicels to which they are affixed transversely at the middle. Leaves – long and stoutly petiolate, the blade elliptical or ovate-oblong, 3-7 cm long, obtuse or sub-acute at the summit, rounded or sub cordate at the base, finally crenulate, thick, greyish-green, vary pubescent, especially on the under surface conspicuously reticulate-veined.\(^{65}\)

**VARIOUS PHARMACOLOGICAL ACTIONS OF SALVIA OFFICINALIS**

**Antioxidant Activity**

Several studies showed the potent antioxidant activity of *Salvia officinalis*. Addition of *Salvia officinalis* extract in the drinking water of rats increased the resistance of rat hepatocytes against oxidative stress. It protected the hepatocytes against dimethoxy naphthoquinone- and hydrogen peroxide-induced DNA damage by increasing glutathione peroxidase activity. The most effective antioxidant constituents of *Salvia officinalis* extract are found to be carnosol, rosmarinic acid, carnosic acid, caffeic acid, rosmanol, rosmadial, genkwanin and cirsimaritin.\(^{66}\)

**Anti-Inflammatory Activity**

It was reported that flavonoids extracted from S. officinalis reduced inflammation in the mouse - carrageenan model and induced analgesic effect in a dose-dependent manner.\(^{66}\) A research showed that topical application of rosmarinic acid inhibits epidermal inflammation. Manool, carnosol, and ursolic acid are the terpenes/terpenoids having anti-inflammatory potential.\(^{66}\)

It was found that the anti-inflammatory action of ursolic acid is twofold more potent than that of indomethacin.\(^{66}\)

**Anti-Cancer Activity**

Extracts of this plant has shown pro-apoptotic and growth-inhibitory effects on cell lines of breast cancer (MCF-7), cervix adeno carcinoma (HeLa), colorectal cancer (HCT-116, HCT15, CO115, HT29), insulinoma (RINm5F), laryngeal carcinoma (HeP-2), lung carcinoma (A549), melanoma (A375, M14, A2058, B16), and oral cavity squamous cell carcinoma. *Salvia officinalis* has antimigratory and antiangiogenic effects as well.\(^{66}\)

The *Salvia officinalis* extract enhances TNF-α and nitric oxide release from macrophages therefore increasing its cytotoxic effect. Rosmarinic acid, a flavonoid of *Salvia officinalis* has been found to inhibit the growth of various human cancer cells including breast adenocarcinoma, colon carcinoma, chronic myeloid leukemia, prostate carcinoma, hepatocellular carcinoma, and small cell lung carcinoma. The anticancer effects of rosmarinic acid could be most probably due to the inhibition of Mitogen-Activated Protein Kinase/Extracellular Signal-regulated Kinase pathway, the suppression of reactive oxygen species (ROS) and nuclear transcription factor-kappa B and the reduction of pro-inflammatory gene cyclooxygenase-2 expression.\(^{65}\)

**Anti-Septic Effects**

The essential oil of *Salvia officinalis* has significant inhibitory effect on the growth of Aeromonas hydrophila, Aeromonas sobria, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumonia, Pseudomonas morganii, Salmonella anatum, Salmonella enteritidis, Salmonella typhi, and Shigella sonnei. The ethanolic extract of *Salvia officinalis* has weak inhibitory effect on Escherichia coli, Pseudomonas aeruginosa, and S. enteritidis.

*Salvia officinalis* has also been reported to show antifungal, antiviral and anti-malarial effects. The antifungal activity has been reported against Botrytis cinerea, Candida glabrata, Candida albicans, Candida krusei, and Candida parapsilosis.\(^{66}\)

**Cognitive and Memory-Enhancing Effects**

Hydroalcoholic extract from *Salvia officinalis* and its main flavonoid rosmarinic acid improved cognition in healthy rats and prevented learning and memory deficits induced by diabetes. *Salvia officinalis* hydroalcoholic extract attenuates morphine-induced memory impairment as well.

Clinical trials also confirmed the results of animal studies and demonstrated that *Salvia officinalis* enhances cognitive performance both in healthy participants and patients with cognitive impairment or dementia.

Moss et al reported that the aroma of *Salvia officinalis* essential oil could enhance prospective memory performance in healthy adults.

On a note to the mechanisms responsible for cognitive and memory enhancing effects of *Salvia officinalis*, a potential interaction with cholinergic system has been shown. It was also found that activation of muscarinic and nicotinic receptors by pilocarpine and nicotine, respectively,
potentiated memory-enhancing effects of *Salvia officinalis*.

*Salvia officinalis* has also been reported to inhibit acetylcholinesterase activity. To date, inhibitors of acetylcholinesterase are the leading therapeutics of Alzheimer’s disease and *Salvia officinalis* might be an important source for developing therapeutic agents for this disease.  

**CONCLUSION**

As it was discussed earlier, plants have different and complex constituents with various activities. Combinations of such plants based on the activity needed can be formulated to form a new synergistic formulation instead of extracting the fractions from it. Such herbal proprietaries have lesser or no side effects than the fractionated and standardised phytochemicals. One such combination can be the above five plants discussed which has certain similar activities and are studied extensively to get a fine and efficacious product.

**REFERENCES**


6. Elisenda Carballido et al., Calendula Plant characteristics, Uses and copying of this document ©Copyright protected. is strictly prohibited


