

Review Article



Various Pharmacological Actions of *Calendula officinalis*, *Tagetes erecta*, *Carica papaya*, *Hypericum perforatum* and *Salvia officinalis*

Rittapalli Bhagya Jyothi^{*1}, Lakshmi Naganathan², Boya Chaitanya³, Akula Naga Venkata Sunitha⁴, V.S.S.S. Gupta Atyam⁵, J.V.C. Sharma⁶

1,5. Department of Pharmacology, Joggipally B.R. Pharmacy College, Moinabad, Telangana, India.

2,6. Department of Pharmacognosy, Joggipally B.R. Pharmacy College, Moinabad, Telangana, India.

3. Department of Pharmaceutics, Joggipally B.R. Pharmacy College, Moinabad, Telangana, India.

4. Department of Pharmaceutical Chemistry, Joggipally B.R. Pharmacy College, Moinabad, Telangana, India.

***Corresponding author's E-mail:** jyopharmaco308@gmail.com

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ABSTRACT

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*.

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 priority.¹

There are various plant metabolites produced in plants. The secondary metabolites and the concentration of them also differs in every plant. There are major differences seen in concentration of constituents within same species but different varieties itself. Each and every such constituent or group of constituents (belonging to same chemical group or different chemical group) have 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. They often interact with the main targets in cells, such as proteins, biomembranes or nucleic acids. Whereas some secondary metabolites appear to have been optimized on a few molecular targets, such as alkaloids on receptors of neurotransmitters, others (such as phenolics and terpenoids) are less specific and attack a multitude of proteins by building hydrogen, hydrophobic and ionic bonds, thus modulating their 3D structures and in

consequence their bioactivities. The multi target activities of many plant metabolites can explain the medical application of complex extracts from medicinal plants for more health disorders which involve several targets.² So, herbs play a vital role in the development of Pharmacology and Pharmacy.

The current review article gives the importance and various pharmacological actions of plants namely *Calendula officinalis*, *Tagetes erecta*, *Carica papaya*, *Hypericum perforatum* and *Salvia officinalis*.

CALENDULA OFFICINALIS



Figure 1: *Calendula officinalis* plant

Calendula officinalis Linn. also called as pot marigold belongs to the family Compositae (Asteraceae). Its Indian native names are *Chamanthipoovu* (Telugu), *Sendigai* (Tamil), *Genda* (Hindi), *Gulsarfi* (Punjabi).^{3,4} The name of this plant comes from a Latin word 'Calend' 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 teeth 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 achene. They have no pappus. The entire plant has a strong unpleasant odour.⁶

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 heptoglobin). 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}

Spasmogenic and Spasmolytic Activity

The aqueous/ethanolic plant extract has shown spasmogenic 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 spasmolytic 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* (ATCC6258), *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 tropica* and *Rhodotorella* spp.²⁰

Glycosides of oleanolic acid and saponins of *Calendula officinalis* showed anti-parasitic activity against *Heligmosomoidespolygyrus*.²¹ Nerolidol of *C. officinalis*



showed anti-malarial activity by inhibiting the parasite to synthesize coenzyme Q in all intraerythrocytic stages.^{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.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 (invitro).²³ Both showed anti-cancerous activity against melanoma (UAAC-62, SK-MEL-5 and LOXIMVI), leukaemia (RPMI-8226 and MOLT-4) and colon cancer (HCC-2998) cell lines.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.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 antihyperlipidemic effects.⁷

TAGETES ERECTA



Figure 2: *Tagetes erecta* plant

Tagetes erecta Linn. also called as Mexican marigold or Aztec marigold belongs to the family Asteraceae. Its Indian native names are *Sthulapushpa* (Samskrit), *Genda*, *Hajara*, *Hajri*, *Jhandu* (Hindi), *Shraavanashya avanthige* (Kannada), *Thulukkaccevvanti* (Tamil), *Banthi* (Telugu), *Tangla* (Punjabi).^{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.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.^{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 Patulintrin as well is one of the potential elements for its antibacterial activity.^{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 parts 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.³⁰

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.^{27,31}

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.^{27,32}

Insecticidal and Mosquitocidal Activity

Nikkon et al reported the insecticidal activity in *Tagetes erecta* flowers against a 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*.³³

Nikkon et al reported the mosquitocidal activity in ethanolic, chloroform and petroleum ether extracts of *Tagetes erecta* 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 erecta* having good mosquitocidal activity.³⁴

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.²⁷

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.³⁵

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.³⁶

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.³⁷

CARICA PAPAYA



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*, *Pappali* (Tamil), *Bappayi* (Telugu), *Kappalam*, *Pappayam* (Malayalam), *Pappangaye*, *Peragi* (Kannada), *Popaiyah*, *Papeetha* (Hindi).³⁸ 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 monoecious 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 (aril).³⁹

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 *Carica papaya* 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.⁴⁰

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.⁴¹

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.⁴²

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)⁴³

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 $55 \times 10^3/\text{ul}$ to $168 \times 10^3/\text{ul}$. 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.⁴⁰

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.⁴²

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.⁴⁰

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.⁴⁰

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.^{45,46}

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.⁴⁴

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).⁴⁷ 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.⁴⁸

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.⁴⁹

The main antibacterial component was determined to be hyperforin.⁵⁰

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.⁵⁰

It was found that 3-hydroxy lauric acid in field-grown *Hypericum perforatum* has anti-HIV activity.⁵¹

Regarding other viruses, an important finding is that hypericin completely inactivated bovine diarrhoea virus in vitro in the presence of light.⁵²

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.⁵³

A research work found that pseudohypericin and hyperforin inhibited production of the inflammatory agent prostaglandin E2 (PGE2).⁵³

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.⁵⁵ Thus, flavonoid extract of *Hypericum perforatum* may effectively treat oxidative stress-related

neurodegenerative disorders such as Parkinson's and Alzheimer's diseases.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.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.⁵⁷

Early research suggested that hypericin 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.^{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.^{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.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.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.⁶²

It was demonstrated that the influx of Na⁺ 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⁺ and Ca²⁺ 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.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.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.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. Schempp 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.⁵²

SALVIA OFFICINALIS



Figure 5: *Salvia officinalis* plant



Salvia officinalis Linn. also called as Common Sage belongs to the family Lamiaceae. Its Indian native names are *Samudraphala*, *shati*, *vrddhadaru* (Samskrit), *Kamrkash*, *Samundarsok*, *Sathi* (Hindi), *Kachori* (Kannada), *Pulam-kizhanma* (Malayalam), *Chimaikkarpuram* (Tamil), *Kachoralu*, *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, 3-7cm 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 cirsimarin.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.⁶⁶

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.⁶⁶

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

- Wadud A, Prasad PV, Rao MM, Narayana A, Evolution of Drug, A Historical Perspective, Bull Indian Inst Hist Med, Hyderabad, Jan-Jun, 37(1), 2007, 69-80.
- Michael Wink, Modes of Action of Herbal Medicines and Plant Secondary Metabolites, Medicines (Basel), Sep, 2(3), 2015, 251–286.
- Anand Kumar Reddy, *Calendula officinalis* Mary gold Banthi Thulukka Saamanthi Zergul, Medicinal Plants – Plants with usage, patents and their publications, 2013, Jan 19. Available from: URL : <http://medplants.blogspot.com/2013/01/calendula-officinalis-mary-gold-banthi.html?m=1>
- Lim T K , Edible Medicinal And Non-Medicinal Plants, Flowers, Volume 7, 213, 432.
- Nelofer Jan, Khurshid Iqbal Andrabi and Riffat John, *Calendula officinalis* - An Important Medicinal Plant with Potential Biological Properties, Proc Indian Natn Sci Acad, 83 No. 4 December 2017 pp, 769-787.
- Elisenda Carballido et al., Calendula Plant characteristics, Uses and Composition, Botanical online, 2019, March 19. Available from : URL : <http://www.botanical-online.com/en/botany/calendula-plant>
- Vrish Ashwlayan et al, Therapeutic Potential of *Calendula officinalis*, Pharm Pharmacol Int J, 6(2), 2018, 149–155.
- Chandran P K and Kutton R, Effect of *Calendula officinalis* flower extract on acute phase proteins, antioxidant defence mechanism and granuloma formation during thermal burns.J Clin Biochem Nutr, 43, 2008, 58-64.
- Leach M J, *Calendula officinalis* and wound healing: A systematic review, Wounds 20, 2008, 1-7.
- Rossiter K, Reid P D, Lwaleed B A, Cooper A J, Voegeli D, Cooper R and Getliffe K, Honey and angiogenesis, 1st International conference on the medicinal uses of Honey, Kota Bharu, Malaysia, 2006.
- Aro A A, Perez M O, Vieira C P, Esquisatto M A M, Rodrigues R A F, Gomes L and Pimentel ER, Effect of *Calendula officinalis* cream on achilles tendon healing.Anat Rec, 298, 2015, 428-435.
- Varlijen J, Structural analysis of rhamnoarabinogalactans and arabinogalactans with immunostimulating activity from *Calendula officinalis*, Phytochemistry, 28, 1989, 2379-2383.
- Wagner H, Proksch A, Riess-Maurer I, Vollmar A, Odenthal S, Stuppner H, Jurcic K, Le Turdu M and Fang Jr, Immunstimulierend wirkende Polysaccharide (Heteroglykane) aus hoheren Pflanzen, Arzneimittel-Forschung 7, 1985, 1069-1075.
- Bashir S, Janbaz K H, Jabeen Q and Gilani A H, Studies on Spasmogenic and Spasmolytic Activities of *Calendula officinalis* flowers, PhytotherRes, 20, 2006, 906-910.
- Rasu M A, Tamas M, Puica C, Roman I and Sabadas M, The hepatoprotective action of ten herbal extracts in CCl4 intoxicated liver, Phytother Res 19, 2005, 744-749.
- Maysa M, El Mallah and Mohamed R A, Hepatoprotective Effect of *Calendula officinalis* Linn (Asteraceae) Flowers Against CCL4 – Induced Hepatotoxicity in Rats., World Appl Sci J 33, 2015, 949-1959.
- Iatsyno A I, Belova L F, Lipkina G S, Sokolov S I and Trutneva E A, Pharmacology of calenduloside B, a new triterpene glycoside from the roots of *Calendula officinalis*, Farmakol Toksikol, 41, 1978, 556-60.
- Preethi K C, Kuttan G and Kuttan R, Anti-inflammatory activity of flower extract of *Calendula officinalis* L and its possible mechanism of action, Indian J Exp Biol 47, 2009, 113-120.
- Hamad M N, Mohammed H J and Merdaw M A, Antibacterial activity of *Calendula officinalis* flowers In vitro Ibn Al- Haitham, J For Pure & Appl Sci, 2011, 243.
- Gazim Z C, Rezende C M, Fraga S R and Svidzinski T I E, Antifungal activity of the essential oil from *Calendula officinalis* L (Asteraceae) growing in Brazil.Braz, J Microbiol, 39, 2008, 61-63.
- Al-Snafi A E, Antiparasitic effects of medicinal plants (part 1)-A review, IOSR J Pharm 6, 2016, 51-66.
- Boyoma F F, Ngouana V, Zollo P H A, Menut C, Bessiere J M, Gut J and Rosenthal P J, Composition and antiplasmodial activities of essential oils from some Cameroonian medicinal plants. Phytochemistry, 64, 2003, 1269-1275.
- Silva E J, Gonçalves E S, Aguiar F, Evencio L B, Lyra M M, Coelho M C, Fraga M C and Wanderley A G, Toxicological studies on hydroalcohol extract of *Calendula officinalis* L, Phytother Res 21, 2007, 332-336.
- Ukiya M, Akihisa T, Yasukawa K, Tokuda H, Suzuki T and Kimura Y, Anti-inflammatory, anti-tumor promoting and cytotoxic activities of constituents of marigold (*Calendula officinalis*) flowers, J Nat Prod, 69, 2006, 1692-1696.
- Sangram Jagtap et al., *Tagetes erecta* orange, India plants.com, 2002, Available from : URL : <https://www.indiaplants.com/plant-details.php?x=CCyVeOENDro>
- Ghani A, Ahmadu Bello University Press, Ltd, Introduction to pharmacognosy, Zaria, Nigeria 1990, 45-17, 187-197.
- Gopi G, Elumalai A and Jayasri P, A concise review on *Tagetes erecta*, Int Journal of Phyto pharmacy Research, Vol 3, Issue 1, 2012, 16-19.
- Basavaraj Chivde V, KarnakumarBiradar V, Rajabhai S, Shiramane, Kamshetty Manoj V, In vitro antioxidant activity studies of the flowers of *Tagetes erecta* L, (Compositae), International Journal of Pharma and Bio Sciences, 2(3), 2011, 223-229.
- Rhama S and Madhavan S, Antibacterial Activity of the Flavonoid Patulin isolated from the flowers of *Tagetes erecta* L, Int Journal of Pharmaceutical Technology and Research, 3(3), 2011, 1407-1409.
- Preeti Verma and Archana Verma, Evaluation of antibacterial activity of different parts of *Tagetes erecta*, Int Journal of Pharmacy & Life Sciences, Vol. 3, Issue 6, June-2012, 1766-1768.
- Patrick Ruddock S, Mario Charland, Sandra Ramirez, Andres Lo'pez, Neil Towers G H, John Arnason T, Mingmin Liao, Jo-Anne Dillon R, Antimicrobial Activity of flavonoids from *Piper lanceae folium* and other colombian medicinal plants against antibiotic susceptible and resistant strains of *Neisseria gonorrhoeae*, Sexually transmitted diseases, 38(2), 2011, 81-88.
- Ranjan Kumar Giri, Anindya Bose and Subrat Kumar Mishra, Hepatoprotective Activity of *Tagetes erecta* against carbon tetrachloride-induced hepatic damage in rats, Acta Poloniae Pharmaceutica n Drug Research, 68(6), 2011, 999-1003.



33. Farjana Nikkon M, Rowshanul Habib M, Ezaul Karim and ZennatFerdousi, Insecticidal activity of flower of *Tagetes erecta* against *Tribolium castaneum* (Herbst), Research Journal of Agriculture and Biological Sciences, 5(5), 2009, 748-753.
34. Farjana Nikkon, M Rowshanul Habib, Zahangir Alam Saud, M Rezaul Karim, *Tagetes erecta* Linn and its mosquitocidal potency against *Culex quinquefasciatus*, Asian Pacific Journal of Tropical Biomedicine, 1(3), 2011, 186-188.
35. Muhammad Arshad Hussain, Tariq Mukhtar and Muhammad Zameer Kayani, Combined wound healing activity of *Gymnema sylvestre* and *Tagetes erecta* Linn, International Journal of Pharmaceutical Applications, 2(2), 2011, 135-140.
36. Bashir S, Gilani AH, Studies on the antioxidant and analgesic activities of Aztec marigold (*Tagetes erecta*) flowers, Phytotherapy Research, 22, 2008, 1692-4.
37. Marcia M, Marques M, Selene M, Moraislcaro G, Vieira P, Mariano G, Vieira P, Ana Raquel, Silva A, Raimundo Rafael De Almeida, Maria Izabel Guedes F, Larvicidal activity of *Tagetes erecta* against Aedes aegypti, Journal of the American Mosquito Control Association, 27(2), 2011, 156-158.
38. Aravind HC, *Carica papaya*, Aravind Herbal Labs, Available from : URL : <http://www.aravindhherbal.com/carica-papaya.html>
39. James A.Duke, *Carica papaya* L, Handbook of Energy Crops, July 3, 1996, Available from : URL : https://hort.purdue.edu/newcrop/duke_energy/Carica_papaya.html
40. Natarajan Sudhakar, Theivanai Vidhya RM, Potential Medicinal Properties of *Carica Papaya* Linn - A Mini Review, IJPPS, Vol 6, Issue 2, 2014.
41. Amit Gupta, Samrat S Patil, Nilima Pendharkar, Antimicrobial and anti-inflammatory activity of aqueous extract of *Carica papaya*, J Herbed Pharmacol, 6(4), 2017, 148-152.
42. Vijay Yogiraj, Pradeep Kumar Goyal, Chetan Singh Chauhan, Anju Goyal, Bhupendra Vyas, *Carica papaya* Linn, An Overview-International Journal of Herbal Medicine, 2 (5), 2014, 01-08.
43. Giordani R, Gachon C, Moulin-Traffort J and Regli P, A synergistic effect of *Carica papaya* latex sap and fluconazole on Candida albicans growth, Mycoses, 40(11-12), 1997, 429-437.
44. Olagunju JA, Adeneyeb AA, Fagbohunkac BS, Bisugac NA, Ketikuc AO, Benebod AS, Olufowobie OM, Adeoyec AG, Alimic MA, Adeleke AG, Nephroprotective activities of the aqueous seed extract of *Carica papaya* Linn in carbon tetrachloride induced renal injured Wistar rats: a dose- and time-dependent study, Biology and Medicine, 1(1), 2009, 11-19.
45. Uche-Nwachi EO, Mitchell CV, McEwen C, Steroidogenic enzyme histochemistry in the testis of Sprague Dawley rats following the administration the water extracts from *Carica papaya* seed, Afr J Tradit Complement Altern Med, 8(1), 2011, 69-78.
46. Chinoy NJ, D'Souza JM, Padman P, Effects of crude aqueous extract of *Carica papaya* seeds in male albino mice, Reprod Toxicol, 8(1), 1994, 75-9.
47. Dr. Jagdev Singh, St. John's Wort (*Hypericum Perforatum*), Ayur Times, 2017, April 13. Available from: URL : <https://www.ayurtimes.com/st-johns-wort-hypericum-perforatum/>
48. John H. Biggs, Stephen F. Brauer, Walter F. Ballinger et al., *Hypericum perforatum*, Missouri Botanical Garden Database, Available from : URL : http://www.missouribotanicalgarden.org/PlantFinder/PlantFinder_Details.aspx?kempcode=e198
49. Lenard J, Rabson A, Vanderoef R, Photodynamic inactivation of infectivity of human immunodeficiency virus and other envelope viruses using hypericin and rose bengal: Inhibition of fusion and Syncytium formation, PNAS, 90, 1993, 158-62.
50. Bystrov N S, Chernov B K, Dobrynin V N, Kolosov M N, The structure of hyperforin, Tetrahedron Lett, 32, 1975, 2791-4.
51. Maury W, Price J P, Brindley M A, Identification of light-independent inhibition of human immunodeficiency virus-1 infection through bioguided fractionation of *Hypericum perforatum*, Virol J, 6, 2009, 101.
52. Kenneth M Klemow, Andrew Bartlow, Justin Crawford, Neil Kocher, Jay Shah, and Michael Ritsick, In Benzie IFF, Wachtel-Galor S, Medical Attributes of St. John's Wort (*Hypericum perforatum*), Herbal Medicine : Biomolecular and Clinical Aspects, 2nd edition, Boca Raton (FL), CRC Press/Taylor & Francis, Chapter 11, 2011.
53. Tedeschi E, Menegazzi M, Margotto D, Suzuki H, Forstermann U, Kleinert H, Anti-inflammatory actions of St. John's wort: Inhibition of human inducible nitric-oxide synthase expression by downregulating signal transducer and activator of transcription-1alpha (STAT-1alpha) activation, J Pharmacol Exp Ther, 307(1), 2003, 254-61.
54. Wang X. D, Li J L, Lu Y et al, Rapid and simultaneous determination of nifedipine and dehydro nifedipine in human plasma by liquid chromatography-tandem mass spectrometry, Application to a clinical herb-drug interaction study. J chromatography B AnalytTechnol Biomed Life Sci, 852(1-2), 2007, 534-44.
55. Zou Y P, Lu Y H, Wei D Z, Protective effects of a flavonoid-rich extract of *Hypericum perforatum* L, against hydrogen peroxide-induced apoptosis in PC12 cells, Phytother, Res, 24 (1), 2010, S6-S10.
56. Remick R A, Diagnosis and management of depression in primary care: A clinical update and review, CMAJ, 167, 2002, 1253-60.
57. Suzuki O, Oya M, Bladt S, Wagner H, Inhibition of monoamine oxidase by hypericin, Planta Med, 2, 1984, 272-274.
58. Robbers J, Tyler V E, Tyler's Herbs of Choice: The Therapeutic Use of Phytomedicinals. New York: Haworth Press, 1999.
59. Chavez M. L, Chavez P | Saint John's wort, Hosp Pharm, 32(12), 1997, 1621-32.
60. Jellin J M, Gregory P J, Batz F, Hitchen K, Pharmacist's Letter/Prescriber's Letter Natural Medicines Comprehensive Database, 4th ed. Stockton, CA: Therapeutic Research Faculty, 2002.
61. Muller W E, Singer A, Wonnemann M, Hyperforin-antidepressant activity by a novel mechanism of action, Pharmaco psychiatry, 34, 2001, S98-S102.
62. Treiber K, Singer A, Henke B, Müller W E, Hyperforin activates non-selective cation channels (NSCCs), Br J Pharmacol, 145(1), 2005, 75-83.
63. Leuner K, Kazanski V, Muller M, et al., Hyperforin-a key constituent of St. John's wort specifically activates, TRPC6 channels, FASEB J, 21(14), 2007, 4101-11.
64. Gurcharan Singh, Sage Weed, Flowers of India. Retrieved 2016, August 23, Available from : URL : <https://www.flowersofindia.net/catalog/slides/Sage%20Weed.html>
65. Merle Zimmermann, AHPA Botanical Identity References Compendium, *Salvia officinalis*, American Herbal Products Association, 2015, April 28, Available from : URL : [http://www.botanicalauthentication.org/index.php/Salvia_officinalis_\(leaf\)](http://www.botanicalauthentication.org/index.php/Salvia_officinalis_(leaf))
66. Ahmad Ghorbani and Mahdi Esmaeilizadeh, Pharmacological properties of *Salvia officinalis* and its components, J Tradit Complement Med, 7(4), 2017 Oct, 433-440.

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