REVIEW ARTICLE

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Review on Pharmacological Update: *Calendula officinalis* Linn.

Devansh Mehta[1], Parkhi Rastogi[1], Ankit Kumar[1], Amrendra Kumar Chaudhary[1*]

Abstracts: The plant *C. officinalis* belonging to family *Asteracea/Compositae*, is native to Central Europe and the Mediterranean, it grows readily in sunny locations throughout North America and Europe. There are about 20 species in this genus cultivated by Egypteans, Greeks, Hindus, and Arabs. Calendula grew in European gardens and has been used medicinally since 12th century. Mainly, the flowers were made into extracts, tinctures, balms, salves and applied directly to skin to help heal wounds and to soothe inflamed and damaged skin. In Italian folk medicine Calendula is used as an antipyretic and anti-inflammatory. The reported pharmacological actions of the plant are, angiogenic property having vascular regeneration parameter affirming the said activity, analgesic properties were confirmed in the flower extract of the plant, it was found triterpenoids were mainly responsible to promote anti-inflammatory activity in the plant, due to presence of faradio esters the plant projects anti-oedematous activity, the additional pharmacological activities explored till date are antimicrobial and antibacterial activity, effective treatment in case of breast cancer, antihepatotoxicity activity, genotoxic and antigenotoxic activity, Hepatoprotective and renoprotective activity, antiviral activity, anti-HIV activity, effective in dealing with periodontal infections, ameliorating incidence of myocardial infarction, antioxidant and anti-immunomodulatory activity, effective treatment for acne, prominent anti-gastric ulcer and wound healing property, effective in dealing with bacterial infections in vets. Further studies of having sun protection factor in Calendula officinalis have also been investigated with positive results. The present review is an anthology of the work done on this potential herbal plant, having prospects of wide areas of therapeutic activity, in a way as an important medicinal source.

INTRODUCTION

Healing art using medicinal plants has been in practice since ancient civilization, leading to collection of wealth of knowledge in texts by our ancestors. One such text, *Materia Medica* has preserved the knowledge of useful medicinal plants yet to be explored by the dot com world. The involvement of floral biodiversity in health care has been well acknowledged in different civilizations. Texts such as *Charaka Samhita, Susruta Samhita, Ashtangahridaya (in Ayurveda)*; works by *Agastiyar, Bogar, Pulippani, Kongannar (in Siddha)* lay interesting proofs. Apart from these documented sources, there is a wealth of information and knowledge on the use of plants for health care of the informal sources like, households and native practitioners conglomerating into an indegenious medical data, plus diversification of the use of medicinal plants in healing art. [1-3] In recent years, the interest in folk medicine or Traditional Medicines from different cultures has increased significantly in modern countries, due to the fact that many prescription drugs worldwide have originated from the tropical flora. [4-5] Traditional plants have been used in many parts of world long time ago where they offer a safe, cheap, and reliable alternative to chemical drugs. [6-7] The relatively lower incidence of adverse reactions of plant preparations compared to the modern conventional pharmaceuticals, coupled with reduced cost, is encouraging to mull over plant medicines as an alternative to synthetic drugs. The nature has provided us various medicinal plants which became the storehouse of remedies to cure all ailments of mankind. [8]

India has a rich flora that are widely distributed throughout the country. Herbal medicines have been the basis of treatment and cure for various diseases and physiological conditions in traditional methods practiced such as Ayurveda, Unani and Siddha. [9-11]

[1]Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University, Meerut-250005, UP.
E-mail: amrendrapharma@gmail.com
*Corresponding author

CALENDULA OFFICINALIS

Calendula has long been used for medicinal purposes; the Romans used the juice from fresh flower parts as a cure for warts, for treatment of jaundice plus a substitute for saffron in the treatment of measles and small pox. [12].

Figure 1: *Calendula officinalis*

C. officinalis also known as Garden Marigold, God-Bloom, Holligold, Marigold, Marybud, and Pot Marigold, belongs to botanical family of Asteraceae or Compositae (from the family of daisy). [13] The parts of the plant, dried flowers used as spice is well thought out as generally recognized to be safe by the Food and Drug Administration along with FEMA known as Flavours and Extracts Manufacturers Association. Traditionally, it is used topically as a natural anti-inflammatory medicine and for poorly healing wounds and leg ulcers. The dosages have been cited are 2–4 ml of tincture diluted to 250–500 ml with water or 2–5 g of herb in 100 g of ointment. [14-15] Other topical uses incorporate treatment for 1st degree burns and scalds, bruises, boils, and rashes. A tea made from 1 to 2 g of the flower in 150 ml of boiling water has

Table 1: Chemical Constituents

Components Class	Major fraction and % Concentration	Sub-fraction
Mineral matter	Major elements as salts	Potassium (6%), Sodium (1.7%), Magnesium (0.9%), Calcium (0.5%), Iron (0.15%)
Carbohydrates	12-25 % dry matter	Arabinoglactan PS II 25 kDa (arabinose, galactose), Arabinoglactan PS III 35 kDa (arabinose, galactose), Mucilage
Lipids	Fatty acids mainly as esters (5% dry weight)	9-Hydroxy-trans-10,cis-12-octadecadienic-acid, Capric acid,Caprylic acid, Dimorphecolic acid,lauric acid, Linoleic acid, Linolenic acid, Myristic acid, Palmitic acid, Palmitoleic acid, Pentadecanoic acid, Stearic acid, Calendic acid
	Hydrocarbon/paraffin/waxes (0.015 % fresh petals)	Dotriacontane,Hentriacontane,Heptacosane,Hexacosane,Nonacosane, Octacosane,Tetratriacontane, Tritriacontane
Phenolic compounds	Phenolic acids in free and esterified forms (0.1%) dry matter	Lignin, Caffeic acid, Chlorogenic acid, Coumaric acid, Ferulic acid, Gentisic acid, *trans-O*-Coumaric acid, O-Hydroxyphenyl acetic acid, 4-Coumaric acid, 4-Hydroxy benzoic acid, Protocatechuic acid,Quinic acid, Salicylic acid (traces),Sinapinic acid, Syringic acid, Vanillic acid, Veratric acid
	Flavanoids (<1.5%)	Astragalin, Hyperoside, Calendoflaside, Calendoflavoside, Calendoflavobioside, Isoquercitrin, Isorhamnetin, Isorhamnetin-3-neohesperidoside, Isorhamnetin-3-*O*-(2//,6// -dirahmnosyl)-glucoside, Isorhamnetin-3-*O*-(2//-rahmnosyl)-glucoside, Isorhamnetin-3-*O*-glucoside, Isorhamnetin-3-ra-rahmnosyl-(1,2)-rahmnoside, Isorhamnetin-3-β-D-glucopyranosyl—6-1-β-1-rhamnofuranoside, Kaempferol, Manghaslin, Narcissin, Neohespiridin, Quercitin, Quercitin-3-neohespiridoside,Rutin
	Tannins (6-10%)	Pyrogallol, Catechol
	Coumarins	Esculetin, Scopoletin,Umbelliferon (7-Hydroxycoumarin)
Steroids and terpenoids	Sterols and Steroids (0.2%)	24-Methylcholest-5, 22-dien-3-β-ol, Stigmasterol, α1-Sitosterol(citrostadeniol), β-Sitosterol, Carvone , Geranylacetone, γ-Terpinene, Linalool,Menthone, 4-Cymene, Sabinene , Terpinenol-4, α-Pinene, α-Terpineol, α-Thujene , Isomenthone, Aloaromadendrol
	Free and esterified triterpinic alcohol (<5%)	Arnidiol, Calenduladiol (fatty acid esters), Erythrodiol, Longispinogenin, Lupentriol, Lupeol and its esters, Maniladiol, Olean-12-ene-3-beta, 16-beta, 28-triol, Taraxasterol
	Triterpenic glycosides (2-10 % dry weight)	Calendulaside – B, A –H (Oleanolic acid glycosides), Calendulasaponins A, B and C (Oleanolic acid glycosides)
Tocopherols		7-Methyltocol, 5,7-dimethyltocol, 5 –Methyltocol, 8-Methyltocol, alpha-tocopherol (=Vitamin E), beta-tocopherol,gamma-tocopherol
Quinones (mainly as polyprenyl quinones)		5-Phytyltoluquinone, 6-Phytytoluquinone, alpha-tocopherolquinone
Carotenes (3 – 5 %)		Beta-Carotene, zeta-Carotene, Lycopene, Lutein, Citroxanthin, Flavoxanthin, Violaxathin, Rubixanthin.
Amino Acids		Alanine, Arginine, Aspartic acid, Aspargine, Valine, Histidine, Glutamic acid, Leucine, Lysine, Proline, Serine, Tyrosine, Threonine, Methionine and Phenylalanine.[34]
Carotenoids	As extracted from Methanol solvent	Neoxanthin, 9z-Neoxanthin, violaxanthin, flavoxanthin, mutatoxanthin, 9Z-anthroxanthin, lutein, 9/9' A- lutein, β- Cryptoxanthin, lycopene.
Volatile oils		α-thujene, α-pienene, sabinene, β-pienene, limonene, 1,8- cineol, p-cymene, trans-β-ocimene, γ-terpenene,δ-3-carene,nonanal,terpene-4-ol,3-cyclohexene-1-ol,α-phellandrene,α-terpeneol, geraniol.

also been used up to three times a day as an antispasmodic. Other oral uses include alleviation of the discomfort associated with stomach ulcers and inflammation of the oral and pharyngeal mucosa. In cosmetic or personal care preparations calendula extracts are used as skin conditioning agents at concentrations ranging up to 1% but are generally below 0.1%. Calendula is recognized as traditional medicine by the European Medicine Agency.

Many Calendula species have a characteristic scent or taste caused by mono- and sesquiterpenes within the essential oil, which in many cases are the reason for their application in folk medicine. [16] *C. officinalis* can be used as a colorant because it majorly contains two classes of pigments, the flavonoids and carotenoids, which can be used as yellow and orange natural colors, respectively. Natural colors are gaining considerable attention since several synthetic colorants have given rise to allergic, toxic and carcinogenic effects. [17-18] Flavonoids have antioxidant activities which play an important role in food preservation and human health by combating damage caused by oxidizing agent. Carotenoids are important to humans and other animals as precursors of vitamin A and retinoids. In addition, they act as antioxidants, immunoenhancers, inhibitors of mutagenesis and transformation, inhibitors of premalignant lesions, screening pigments in primate fovea, and non-photochemical fluorescence quenchers. [19-24]

In Europe, the leaves are considered as resolvent and diaphoretic while the flowers are used as a stimulant,

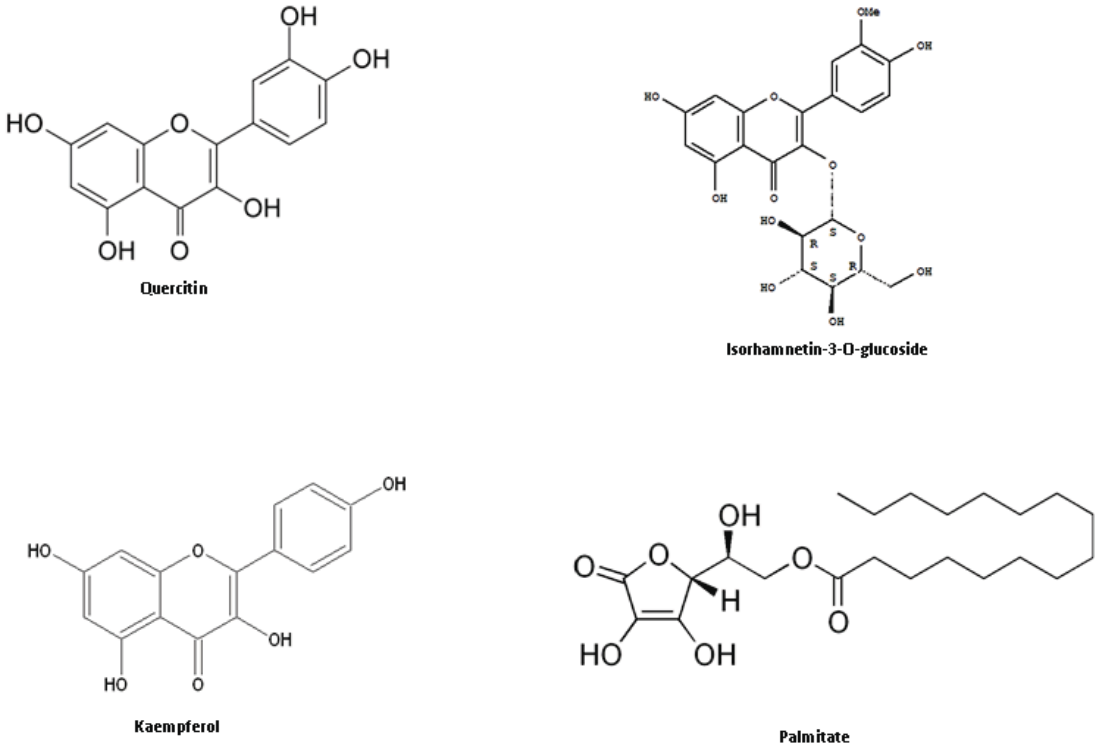

Figure 2: Structures of main constituents

antispasmodic and emmenagogue. In England, the decoction of the flowers was used as a posset drink for the treatment of measles and smallpox, and the fresh juice as a remedy for jaundice, costiveness (constipation) and suppression of the menstrual flow. In India, the florets are used in ointments for treating wounds, herpes, ulcers, frostbite, skin damage, scars and blood purification. The leaves, in infusion, are used for treating varicose veins externally. [25]

Scientific Classification [26]

C. officinalis belongs to:

- Kingdom : Plantae
- Subkingdom: Tracheobionta
- Division : Magnoliophyta
- Class : Mangnoliopsida
- Subclass : Asteridae
- Order : Asterales
- Family : Asteraceae
- Tribe : Calenduleae
- Genus : Calendula
- Species : *Calendula officinalis*

Morphology

The plant is an annual, seldom biennial. It grows to between 30 and 50 cm high, and has about 20 cm long tap root and numerous thin, secondary roots. The stem is erect, angular, and downy and branched from the base up or higher, tip of each stem, there is a 5 to 7 cm composite flower head, consisting of an epicalyx of numerous narrow-lanceolate sepals, which are densely covered on both sides with landular hairs. The alternate leaves are almost spatulate at the base, oblong to lanceolate above and are all tomentosae. The inner section of the flower head is made up of orange-yellow tubular florets. The disc florets are pseudohermaphrodites but the female is sterile. The zygomorphic ray florets at the edge are female, their stamens are completely absent, and their inferior ovaries are much more developed than those of the tubular florets. The fruit forms only in the female ray flowers. The heterocarp achenes are sickle-shaped, curved and ringed. [27-29]

Phytoconstituents

The main phytoconstituents found in *C. officinalis* are steroids, terpenoids, free and esterified triterpenic alcohols, phenolic acids, flavonoids (quercetin, rutin, narcissin, isorhamnetin, kaempferol), and other compounds. [30]

The phytochemical constituents varies in different extracts of *C. officinalis*, petroleum ether extract contains triterpenes and fatty acids; the methanolic extract contains carbohydrates, glycosides, saponins, triterpenes, fatty acids, and diterpenes; the ethanolic extract contains carbohydrates, glycosides, saponins, triterpenes, fatty acids, diterpenes; and the aqueous extract contains carbohydrates, glycosides, saponins, triterpenes, flavanoids, and diterpenes. [31]

Different chemical constituents of *C. officinalis* [32] are mentioned in Table 1.

PHARMACOLOGICAL UPDATE

Calendula, too known as Zergul reported to have sesquiterpenes, flavonoid glycosides, triterpenoid saponins, triterpene alcohols, phenolic acids, sterols, calendulin and bitters as pharcological significant constituents. The triterpene alcohols have shown to incur

anti-inflammatory activity. A report on Calendula compiled by (*Kemper et al.1999*), chalks out effectiveness in gastrointestinal/ hepatic disorders, potential sedative acting upon neuro psychiatric anatomy, having estrogenic and uterotonic effects, potential immunostimulant anti-inflammatory, positive anti-bacterial, anti-viral, and anti-fungal. [11] The following paragraphs would lay emphasis on diversification of activity from angiogenic, anti-inflammatory, anti-microbial, anti-viral, to the wound healing and cancer prospect of the plant *C.officinalis* holds, and its significance to the therapeutic society.

Angiogenic Activity

(*Parente et al., 2011*) carried out experiment on different models using rats and embryonated eggs to evaluate healing and angiogenic activities of extracts and fractions of the plant, through the induction of skin wounds and the chorioallantoic membrane, respectively. Vascular proliferation was chosen as parameter to verify the intensity of expression of vascular endothelial growth factor in cutaneous wounds of rats. The angiogenic activity of the extract and the fractions was evidenced in both experimental models. The positive effect of angiogenesis, characterized by the induction of neovasxularization is healing action. [33]

Analgesic Activity

(*Behtash et. al., 2003*) took the hydro alcoholic extract of *calendula* flowers and evaluated for the analgesic activity using formalin and writhing test. The tests were performed using morphine (2.5 mg/kg s.c) and hydroalcoholic extract of the test. The test results emphasized significance of *C. officinalis's* analgesic activity. [34]

Anti-inflammatory Activity

(*Preethi et.al., 2009)* carried out anti-inflammatory activity on *C. officinalis* flower extract against carrageenan and dextran-induced acute paw edema. Moreover, increased levels of proinflammatory cytokines IL- 1beta, IL-6, TNF-alpha and IFN-gamma and acute phase protein, C- reactive protein (CRP) in mice produced by LPS injection were inhibited significantly by the extract. LPS induced cyclooxygenase-2 (Cox-2) levels in mice spleen were also found to be inhibited by extract treatment. The results showed that potent anti-inflammatory response of *Calendula officinalis* extract may be mediated by the inhibition of proinflammatory cytokines and Cox-2 and subsequent prostaglandin synthesis. [35]

(*Hamburger et. al., 2003)* found phytoconstituents namely, faradiol 3-O-laurate, palmitate and myristate, as major anti-inflammatory triterpenoid esters in the flower heads of the medicinal plant Calendula officinalis. [36]

(Ukiya et al., 2006) found ten oleanane-type triterpene glycosides, including four new compounds, calendulaglycoside A 6'-O-methyl ester, calendulaglycoside A 6'-O-n-butyl ester , calendulaglycoside B 6'-O-n-butyl ester, and calendulaglycoside C 6'-O-n-butyl ester, along with five known flavonol glycosides, were isolated from the flowers. [37]

Anti-oedematous Activity

(*Zitterl-Eglseer et al., 1997)* carried out anti-odematous activity using flower heads of *C. officinalis*, Asteraceae and found faradiol esters (1, 2); mainly faradiol-3-myristic acid ester, faradiol-3-palmitic acid ester and psi-taraxasterol (having slightly lower effect), separated and isolated by column chromatography and HPLC, as effective anti-oedematous agent. [38]

Antimicrobial Activity and Antibacterial Activity

(*Roopashree et al., 2008)* found the antimicrobial potential of the plant extracts against the test organisms using the agar gel diffusion susceptibility test. All the bacterial pathogen used in this work demonstrated susceptibility to the Ethanol, Distilled water and n-Butanol extracts of *Calendula officinalis.* Ethanol extract gave the highest zone of inhibition (35.5mm) on *Escherichia coli*. The result were, with Cogulase (+) *Staphylococci* showed the highest zone of inhibition i.e. 30.2 mm in diameter, Cogulase(-) *Staphylococci* showed the highest zone of inhibition i.e. 35.0mm in diameter, with *Pseudomonas aeruginosa* the highest zone of inhibition was 27.5 mm in diameter, with *Enterococcus sp.* Highest zone of inhibition recorded was 30.2 mm in diameter, with *Candida albicans and Candida parapsilosis* it showed the highest zone of inhibition i.e. 24.0 mm and 24.5 mm in diameter respectively. The observation that *C. officinalis* has good inhibition against *E. coli, P. aeruginosa, Enterococcus sp., Cogulase (+) Staphylococcus sp., Cogulase (-) Staphylococcus sp., C. albicans* and *C. parapsilosis* tends to prove worthy remedy to the problem of drug resistance against these pathogens which are already known to be resistant to the most of the standard antibiotics (Penicillin, Tetracycline, Erythromycin, Streptomycin, Fluconazole and Amphotericin B) thus *C. officinalis* showed effective results against most of the resistant organisms. It is interesting to note that the action of the extracts of *C. officinalis* is non toxic. Studies have shown that the alcohol and water based extracts of the plant have very low toxicity in mammals. [31]

(*Goyal et. al., 2011*) showed the antibacterial activity in the plant and found the effectiveness of different solvents and the extracts against both gram positive and gram negative organisms by cup plate technique. Among the various extracts, aqueous extracts were found to be more effective against all the bacteria. *Staphyllococcus aureus* was more susceptible to the aqueous extracts among the tested organisms. [39]

Effect on Breast Cancer

(*Pommeir et al., 2004*) carried out single blinded, randomized phase III study using *C. officinal* is with trolamine in 254 women receiving radiation for breast cancer. The test was carried out using formulation creams of *C. officinalis* and the results were found to be effective. [40]

Anti-hepatotoxicity Activity

(*Barajas et al., 2006*) carried out tests using 344 male rats to check the hepatoprotective activity from the extracts of

C. officinalis. The protective effect of *Calendula officinalis* started at 0.1 mg/kg concentration, increased at 0.5 mg/kg and reached its maximum at 2.5 mg/kg, when it decreased the area and number of altered foci by 55 % and 49 %, respectively, in comparison with rats treated only with carcinogen. The test results were effective against the rat liver cells. [41]

Genotoxic and Anti-genotoxic Activity

(Pérez-Carreón et al., 2002) found the genotoxic and antigenotoxic activity in the flowers of *C. officinalis* and found flavanols having wound healing property. The test was mainly to see whether *C.officinalis* extracts induce unscheduled DNA synthesis in rat liver cell cultures, and if these extracts can reverse diethylnitrosamine (DEN)-induced UDS. Four different flower extracts were prepared: aqueous (AE), aqueous-ethanol (AEE), ethanol (EE) and chloroform (CE). Concentrations producing genotoxic damage were three orders of magnitude above concentrations that conferred total protection against the DEN effect. Thus, at the lower end, ng/ml, concentrations of the two polar extracts AE and AEE conferred total protection against the DEN effect and at the higher end g/ml, concentrations produced genotoxic effects. These results justify the study of *Calendula officinalis*flower extracts to obtain products with biological activity and to define their genotoxic or chemopreventive properties. [32, 42]

Hepato-protective and Reno-protective Activity

(*Preethi et al., 2009)* evaluated hepatoprotective effects in flower extract of *Calendula officinalis* against CCl4 induced acute hepatotoxicity and cisplatin induced nephrotoxicity. The activities of serum marker enzymes of liver injury like glutamate pyruvate transaminase (SGPT), glutamate oxaloacetate transaminase (SGOT) and alkaline phosphatase (ALP) which was increased by CCl4 injection was found to be significantly reduced by the pretreatment of the flower extract at 100 and 250 mg/kg body weight. The lipid peroxidation in liver, the marker of membrane damage and the total bilirubin content in serum were also found to be at significantly low level in the extract pretreated group, indicating its protective role. The kidney function markers like urea and creatinine were significantly increased in cisplatin treated animals. However, their levels were found to be lowered in the extract pretreated groups (100 and 250 mg/kg body weight). Moreover, cisplatin induced myelosuppression was ameliorated by the extract pretreatment. Treatment with the extract produced enhancement of antioxidant enzymes--superoxide dismutase and catalase and glutathione. Results suggest a protective role of the flower extract of Calendula officinalis against CCl4 induced acute hepatotoxicity and cisplatin induced nephrotoxicity. Extract has been found to contain several carotenoids of which lutein, zeaxanthin and lycopene predominates. Possible mechanism of action of the flower extract may be due to its antioxidant activity and reduction of oxygen radicals. [43]

Antiviral Activity

(*Bogdanova et al., 1970)* conducted study on Herpes simplex, Influenza A_2 and Influenza APR_8 virus's *in-vitro* and found the extracts of flowers of *C. officinalis* as effective agent against these viruses. [44]

Anti – HIV Activity

(*Kalvatchev et al., 1997)* examined Anti-HIV activity in the extracts of dried flowers from *Calendula officinalis* for their ability to inhibit the human immunodeficiency virus type 1 (HIV-1) replication. Both organic and aqueous extracts were relatively nontoxic to human lymphocytic Molt-4 cells, but only the organic one exhibited potent anti-HIV activity in an in vitro MTT/ tetrazolium-based assay. In addition, in the presence of the organic extract (500 micrograms/ml), the uninfected Molt-4 cells were completely protected for up to 24 h from fusion and subsequent death, caused by co-cultivation with persistently infected U-937/HIV-1 cells. It was also found that the organic extract from *C. officinalis* flowers caused a significant dose- and time-dependent reduction of HIV-1 reverse transcription (RT) activity. An 85% RT inhibition was achieved after a 30 min treatment of partially purified enzyme in a cell-free system. These results suggested that organic extract of flowers from C. officinalis possesses anti-HIV properties of therapeutic interest. [45]

Effects on Human Gingivitis Fibroblasts

(*Saini et al., 2012)* found most abundant esters in *C. officinalis,* mainly, lauryl, myristoyl, and palmitoyl esters. Quercetin, an active component of Calendula, decreases the expression of tumor necrosis factor-a (TNF-a), interleukin-b (IL-1b), IL-6 and IL-8 in phorbol 12-myristate 13-acetate and calcium ionophore-stimulated human mast cells. Quercetin, an active component of Calendula, decreases the expression of tumor necrosis factor-a (TNF-a), interleukin-b (IL-1b), IL-6 and IL-8 in phorbol 12-myristate 13-acetate and calcium ionophore-stimulated human mast cells. Quercetin has been shown to inhibit recombinant human matrix metalloproteinases (MMPs) such as MMP-1,10 MMP-2 and MMP-9. The MMPs constitute a family of over 25 structurally related, but genetically distinct proteolytic enzymes that can process or degrade numerous extracellular, pericellular and non-matrix substrates. They have been implicated in periodontal disease. Periodontal disease is a chronic inflammatory disease of the attachment structures of the teeth. It is one of the most significant causes of tooth loss in adults and the most prevalent form of bone pathology in humans, as well as it is a risk factor for systemic health issues. In periodontal disease, the MMPs have been reported to be involved in gingival extracellular matrix (ECM) degradation. Increased levels of the MMPs have been detected in gingival tissues, as well as in the gingival crevicular fluid from patients affected with periodontal disease. Fibroblasts, a major cell type in gingival connective tissues, express multiple MMPs. Fibroblasts have a central role in the homeostasis, pathogenesis and healing of the gingival tissues. The breakdown of gingival collagen fibers in periodontal soft

and hard tissues (alveolar bone resorption) by the action and cascade of both the MMPs and cytokines/growth factors contributes to the clinical signs and treatment outcomes of periodontal disease. It is believed that systemic pharmaceuticals capable of inhibiting the MMPs could be very useful as an adjunctive treatment/ medication in periodontal disease. One such systemic pharmaceutical is a 'sub-antimicrobial dose' of doxycycline (Periostat, Collagenex, Newton, PA), which is administered as a 20 mg tablet. Periostat is approved and indicated as an adjunct to scaling and root planing in the treatment of chronic periodontitis. The main action of Periostat is to inhibit MMP activity. Identifying other therapeutic agents that has the similar mechanisms ofaction could offer more choices in the treatment of periodontal disease and avoid the possible side-effects of antibiotics such as antibiotic resistance. Therefore, the purpose of this study was to examine the in vitro effects of Calendula extract on human gingival fibroblast (HGF) mediated collagen degradation and MMP-2 activity. [46]

Amelioration of Myocardial-infarction

(*Ray et al., 2010)* found that at a relatively high dose, calendula can lower blood pressure and cholesterol. Since inflammatory responses are behind many cardiac diseases, it leads to evaluate, if calendula could be cardioprotective against ischemic heart disease. The plant extract achieved cardio protection by stimulating left ventricular developed pressure and aortic flow as well as by reducing myocardial infarct size and cardiomyocyte apoptosis. Cardioprotection appears to be achieved by changing ischemia reperfusion-mediated death signal into a survival signal by modulating antioxidant and anti-inflammatory pathways as evidenced by the activation of Akt and Bcl2 and depression of TNFα. The results further strengthen the concept of using natural products in degeneration diseases like ischemic heart disease. [47]

Anti-oxidant Effect

(*Braga et al., 2009)* examined whether a propylene glycol extract of *Calendula officinalis*interferes with ROS and RNS during the PMN respiratory bursts, and to establish the lowest concentration at which it still exerts antioxidant activity by means of luminol-amplified chemiluminescence. Electron paramagnetic resonance (EPR) spectroscopy was also used in order to confirm the activity of the *Calendula officinalis* extract. The Calendula officinalisextract exerted its anti-ROS and anti-RNS activity in a concentration-dependent manner, with significant effects being observed at even very low concentrations: 0.20 µg/ml without L-arginine, 0.10 µg/ml, when L-arginine was added to the test with phorbol 12-myristate 13-acetate and 0.05 µg/ml, when it was added to the test with N-formyl-methionyl-leucyl-phenylalanine. The EPR study confirmed these findings, 0.20 µg/ml, lowest concentration of *C. officinalis* extract significantly reduced 2, 2-diphenyl-1-picrylhydrazyl. These findings are interesting for improving the antioxidant network and restoring the redox balance in human cells with plant-derived molecules as well as extending the possibility of antagonizing the oxidative stress generated in living organisms when the balance is in favor of free radicals as a result of the depletion of cell antioxidants. [48]

Anti-immunomodulatory Activity

(*Marina et al., 2007)* found a number of immunomodulatory effects have been attributed to the medicinal plants *C. officinalis* and *Echinacea angustifolia*; however, little is known about whether treatment with these plants can enhance antigen-specific immunity. The experiment was carried out on 28 Leghorn hens. The *Calendula officinalis* extraction induced a gradually increasing specific humoral activity, persistent after the stimulation, during both primary and booster vaccination. The active principles in the *Calendula* extraction positively influenced the anti-Newcastle antibody titers, without attaining the values in the control groups. [49]

Activity on Acne

(*Ibrahim Zh et al., 2010)* found that variety of herbs, such as Tea tree, Aloe Vera, Neem, Tulsi, Marigold, Sea buck thorn, Turmeric etc. are used to treat acne. These are very safe and effective. Different hydroalcoholic extracts of *C. officinalis* possessed antimicrobial, antifungal and antiviral properties against *S. aureus* and *S. fecalis, P.gingivalis, F.nucleatum, C.gingivalis, V.parvula, E.corrodens, P.micros and A.odontolyticus.* The research lays emphasis on flavonoids showing anti-acne effect at the concentration of 0.04%. [50-51]

Hypoglycaemic and Gastric Ulcer Activity

(*Yoshika et al., 2001)* found that methanolic extract and its 1-butanol-soluble fraction from the flowers of *C. officinalis* to showed a hypoglycemic effect, inhibitory activity of gastric emptying, and gastroprotective effect. From the 1-butanol-soluble fraction, four new triterpene oligoglycosides, calendasaponins A, B, C, and D, was isolated, together with eight known saponins, seven known flavonol glycosides, and a known sesquiterpene glucoside. Their structures were elucidated on the basis of chemical and physicochemical evidence. The principal saponin constituents, glycosides A, B, C, D, and F, exhibited potent inhibitory effects on an increase in serum glucose levels in glucose-loaded rats, gastric emptying in mice, and ethanol- and indomethacin-induced gastric lesions in rats. [52]

Wound Healing Activity

(*Parente et al., 2012)* studied the ethanolic extract, the dichloromethane, and hexanic fractions of the flowers from plants growing in Brazil to show wound healing activity in rat models. The angiogenic activity of the extract and fractions was evaluated through the chorioallantoic membrane and cutaneous wounds in rat models. The healing activity of the extract was evaluated by the same cutaneous wounds model through macroscopic, morphometric, histopathologic, and immune-histochemical analysis. [53]

Veterinary Uses

(*Stear et al., 2007)* studied the antihelmentic activity of *C. officinalis* and found effective against the *H. bakeri* larvae.[54-55]

(*Lans et al., 2007)* studied the antihelmintic activity on *C.officinalis* and group of other plants like, *Artemisia cina* O. Berg, *Mentha piperita* L., *Salvia officinalis*, etc. They found during their study *C .officinalis* flowers effective in intestinal worms and amoebial infections. [56]

Current Medicinal Portfolio

C.officinalis is used in homeopathic as chief medicinal agent for wound healing. It is used as an external and internal medicine for painful, open sores, cuts, as a hair tonic to treat dandruff and lice, distilled calendula as vaginal instillations in leucorrhoea, as constitutional remedy in erysipelas. [57]

Various market preparations having *C.officinalis* extract are available; Ayurvedic and Homeopathic companies have launched market preparations to be used for their respective therapeutic benefits.

CONCLUSION

Calendula officinalis also known has Marigold, is just an example, of the diversity of medicinal plants hold in the Medicine World. The therapeutic areas covered by *C. officinalis*, showing promising activity, signifies its importance, to drug industry. Even the areas which are not fully treatable, like Aids, have some promising curing signals from the plant itself. Not only in Humans, but it also, finds significance in Animals. *Calendula officinalis* is thus, one of the medicinal plants, which shall be put into use widely across Industry.

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