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Beneficial effects of *Perilla frutescens* that can be explored as health food-A review

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ABSTRACT

Perilla frutescens is used as spices, condiments, leafy vegetables and herbal medicines in many parts of the world including India especially in the north eastern region where the traditional used of *P. frutescens* in culinary recipes is well known. Various studies presented herein showed the plant has potent anti-inflammatory, anti-oxidant, anti-microbial, anti-allergic and anti-proliferative activities that could be explored for therapeutic use.

Perilla frutescens belongs *to Lamiaceae* family. It is an annual aromatic plant cultivated and widely consumed in most Asian countries. Modern research has revealed that different plant parts of *P. frutescens* possess enormous amounts of bioactive secondary metabolites, including terpenoids, flavonoids, alkaloids, steroids, quinines and phenolic compounds, which exhibit a wide range of biological activities and have immense potential applications as pharmaceuticals, nutraceuticals, agrochemicals, biopesticides, flavours, fragrances, colours, and food additives (Hou *et al*., 2022). Here, we present some of the research work highlighting the activities and effects of *P. frutescens* that confers beneficial effects on health.

1. Introduction

Anti-inflammatory effects

P. frutescens is a dietary leafy herb consumed as a traditional condiment as well as used in traditional medicine for its anti-inflammatory activity. The terpenoids and alkaloids of *P. frutescens* showed remarkable inhibitory effect on the production of inflammatory mediator- nitric oxide (NO) and pro-inflammatory cytokines (TNF-α and/or IL-6) in LPS-stimulated RAW264.7 cells (Wang *et al*., 2018) while the aqueous extract of *P. frutescens* showed stronger TNF-α suppressing activity than ether extract (Lin *et al*., 2016). Different terpenoids compound identified from ethanol extracts of the leaves were evaluated for their inhibitory effects on 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear inflammation in mice and found all the compounds tested showed a marked anti-inflammatory effect (Banno *et al*., (2004). Rosmarinic acid (RA) of *P. frutescens* extracts potently inhibited the release of HMGB1 and down-regulated HMGB1-dependent inflammatory responses in human endothelial cells. It also inhibited HMGB1-mediated hyper permeability and leukocyte migration in mice (Yang *et al*., 2013). The cytokines such as TNF-α, IL-1β and IL-6 are pivotal for provoking airway inflammation. Ethanol extract of the leaves of *P. frutescens* was found to clearly inhibit TNF-α production in the mice lung while phenylpropanoids like elemicin and myristicin were found to concentration-dependently inhibit IL-1β-treated IL-6 production from lung alveolar epithelial cells (Lim *et al*., 2014). A polyphenolic flavonoid, luteolin inhibited the secretion of IL-1β and TNF-α from human mast cells (HMC-1) in a dose-dependent manner (Kwon *et al*., 2014). It also inhibited the NO production in LPS-activated microglia in a dose-dependent manner and suppressed the degradation of I-κB-α. The expression of protein and mRNA of iNOS in LPS-activated microglia may have beneficial effects in the treatment of neuro-inflammatory diseases through the inhibition of iNOS expression (Kim *et al*., 2006). Inhibitors - neolignans 1 and 2 identified from *P. frutescens* suppressed expression of iNOS enzyme and secretion of TNF-α in LPS - activated RAW 264.7 cells (Ryu *et al*., 2002). Prenyl 3-benzoxepin derivatives - perilloxin and dehydroperilloxin isolated from

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the dichloromethane extract of the stems of *P. frutescens* showed *in-vitro* cyclooxygenase-1 (COX-1) inhibitory activities (Liu *et al*., 2000). Flavonoids purified from the ethyl acetate-soluble fraction of green *P. frutescens* leaves was also found to significantly inhibit NO production in IL-1β-stimulated rat hepatocytes, which have been used to monitor the anti-inflammatory effects of herbal constituents (Nakajima *et al*., 2015). New cultivar of *P. frutescens* developed by gamma irradiated mutation breeding produced higher content of isoegomaketone in leaves that exhibited inhibitory activity on NO production in LPS - activated RAW264.7 cells (Nam *et al*., 2017). Perillaldehyde (PAH), a major component of essential oil of *P. frutescens*, has anti-inflammatory effects in mice indicated by serum IL-6 and TNF-α levels in LPS induced inflammatory activity (Ji *et al*., 2014). The leaves extract inhibited superoxide anion production, elastase release, reactive oxygen species formation, CD11b expression and cell migration on N-formyl-Met-Leu-Phe (fMLF)-stimulated human neutrophils in dose-dependent manners. The anti-inflammatory effects of *P. frutescens* leaf extract (PLE) in murine macrophage RAW264.7 cells indicated it significantly reduced the LPS-induced mRNA expression of the IL-6, IL-8, TNF-α, cyclooxygenase-2 (COX-2) and iNOS genes in a dose-dependent manner. In addition, PLE reduced NO production and PGE2 secretion induced by LPS. It also inhibited activation of mitogen-activated protein kinases (MAPKs), increased the cytosolic IκBα level, and reduced the level of nuclear factor (NF)-κB via the inhibition of extracellular-signal-regulated kinase (ERK)1/2, c-Jun N-terminal kinase (JNK), p38, as well as NF-κB signalling in RAW264.7 cells stimulated with LPS (Huang *et al*., 2014). The PLE effect on dextran sulfate sodium (DSS)-induced colitis in mice showed the serum cytokine TNF-α, IL-17A, and IL-10 were significantly lowered. *In-vitro* analyses of biologically active ingredients showed luteolin suppressed production of proinflammatory cytokines - TNF-α, IL-1β, IL-6, and IL-17A, while apigenin suppressed secretion of IL-17A and increased the anti-inflammatory cytokine IL-10 and RA increased the regulatory T cell population (Urushima *et al*., 2015). The findings suggested that PLE might be useful in treatment and prevention of DSS-induced colitis since the progression of inflammation in vascular diseases relates with the endothelial activation and elevation of endothelial microparticles. Paradee *et al*., (2021) reported PLE have been found to significantly attenuate endothelial activation by decreasing the expression of intracellular adhesion molecule 1 (ICAM-1). The anti-inflammatory effects on activated human neutrophils were mediated through two independent signalling pathways involving SFKs (Src and Lyn) and mobilization of intracellular Ca2+ (Chen *et al*., 2015). These studies suggested that PLE significantly decreases the mRNA expression and protein production of pro-inflammatory mediators and has potential as a therapeutic agent against inflammation.

Antioxidant effects

Naturally occurring antioxidants found in foods have gained grounds to replace synthetic antioxidants to offset the negative side effects of the later (Zheng and Wang, 2001). Antioxidants delay or restrict the cellular formation of reactive oxidizable substrates, and also function to quench the substrates formed during metabolic processes. Green PLE exhibited high antioxidant response element (ARE) activity. The active ingredient responsible for the ARE activity was identified as 2′,3′-dihydroxy-4′,6′-dimethoxychalcone (DDC) which inhibited the formation of intracellular reactive oxygen species and the cytotoxicity induced by 6-hydroxydopamine thereby enhanced cellular resistance to oxidative damage through activation of Nrf2-ARE pathway (Izumi *et al*., 2012). The methanolic extracts of stalk, leaf and seed of *P. frutescens* exhibited reducing power, chelating capacity and capacity to scavenge free radicals in a dose-dependent manner (Lin *et al*., 2007). The antioxidant activity evaluation of seeds revealed that RA and RA-3-o-glucoside were the dominant phenolic antioxidants with strong antioxidant activities (Zhou *et al*., 2014). The RA extract from the leaves and phenolic fraction of the methanolic extracts of seed - caffeic acid, RA and luteolin exhibited significant scavenging abilities against DPPH and ABTS radicals (Kim and Lee, 2019; Li *et al*., 2020). It has been reported that geographical locations, climatic conditions and Perilla varieties influences the variations in different antioxidants capacities (Vasco *et al*, 2008; Sargi *et al*., 2013). Chemical polymorphism in the oils based on cluster analysis and principal component analysis suggested the geographic origin greatly influenced the chemical composition and bioactivities of *P. frutescens* (Tian *et al*., 2014). Therefore, these factors should be considered while developing this promising bioresource to be use as antioxidants in the food and pharmaceutical industries.

Antimicrobial effects

P. frutescens was reported to possess antimicrobial and antifungal activities by various workers. The ether extract of leaves exhibited inhibitory activity against *Escherichia coli*, *Staphylococcus aureus*, *Vibrio parahemolyticus* and *Tricophyton mentagrophytes* @1.0 mg/mL concentration (Lin *et al*., 2016). The essential oils of *P. frutescens* possess antibacterial activity (Burt, 2004) and have been demonstrated against gram positive (*Bacillus subtillus, Porphyromonas gingivales, Propionibacterium*

acnes, Streptococcus mutans, Actinomyces naeslundii), gram negative (*Escherichia coli, Salmonella choleraesuis, Enterobacter aerogenes, Pseudomonas aeruginosa*) bacteria and antifungal including *Aspergillus niger, Aspergillus flavus, Aspergillus oryzae, Rhizopus oryzae, Alternaria alternate, Candida albicans, Candida utilis, Mucor mucedo, Penicillium chryogenum, Sacharomyces cerevisiae* (Kang *et al*., 1992; Tian *et al*., 2014). The phenolic compounds of extract from the seed have antimicrobial activity against oral cariogenic *Streptococci* spp and periodontopathic *Porphyromonas gingivalis* suggesting it may be the source of an antimicrobial agent that could prevent dental caries and periodontal diseases (Yamamoto and Ogawa, 2002). RA extract from the leaves exhibited antimicrobial activity against bacteria and fungi by inhibiting post translation enzymes- peptide deformylase of bacteria and N-myristoyltransferase of fungi which is essential for synthesising functional polypeptides that it could be used to develop pharmaceutical and nutraceutical drug ingredient (Li *et al*., 2020). The aqueous leaf extract was reported to inhibit the SARS-CoV-2 virion replication *in-vitro* by blocking viral RNA and protein synthesis (Tang *et al*., 2021). It was also shown capable of inhibiting enterovirus-A71 and influenza virus suggesting a broad-spectrum inhibition capacity against RNA viruses. The antimicrobial properties of *P. frutescens* shows promising use in the future against various pathogens. Hence identifying the active component in the extracts of leaves, seeds or its oil is essential.

Anti-allergic effects

P. frutescens leaves have shown therapeutic efficacy in the treatment of allergies, bronchial asthma and systemic damage due to free radicals. The PLE significantly suppressed the passive cutaneous anaphylaxis in mice ear which was brought about by rosmarinic acid with a partial contribution from some macromolecular compounds. The anti-allergic titer of RA was more effective than Tranilast, a modern anti-allergic drug (Makino *et al*., 2003).The oral administration of PLE, which contains high amount of RA to treat allergic asthma induced by house dust mite allergen on a murine model significantly prevented the increases in the numbers of eosinophils in bronchoalveolar lavage fluids and in airways. It also inhibited the enhanced protein expression of IL-4, IL-5, eotaxin and allergen-specific IgG1in the lungs of sensitized mice (Sanbongi *et al*., 2004) draws the possibility of effective intervention for allergic asthma. Extract of *P. frutescens* enriched for RA suppresses allergic immunoglobulin responses and inflammation caused by polymorphonuclear leukocytes in mice. It also significantly decreased the numbers of neutrophils and eosinophils in nasal lavage fluid in patients with seasonal allergic rhinoconjunctivitis (Takano *et al*., 2004). The antipruritic properties of luteolin, a polyphenolic flavonoid from the leaves of *P. frutescens* significantly reduced the histamine release from rat peritoneal mast cells stimulated by compound 48/80, a potent histamine liberator. It was also found the administration of luteolin markedly inhibited the scratching behaviour and vascular permeability induced by pruritogens suggesting that luteolin has potential as a therapeutic agent against inflammation and itch-related skin diseases (Jeon *et al*., 2014). The effect of aqueous fraction of *P. frutescens* (PfB/af) on atopic dermatitis induced by 2, 4-dinitrofluorobenzene (DNFB) in animal model revealed that PfB/af (100 µg/ml) exhibited strong anti-atopic dermatitis activity, interceding 35% reduction of the immune response, as measured by the thickness of ear epidermis swelling, and resulting in decreased eosinophil levels (73.7%) in adjacent skin tissues (Heo *et al*., 2011). It was also shown to have both *in-vivo* and *in-vitro* effects on mast cell-mediated immediate-type allergic reactions in rats. The aqueous extract of *P. frutescens* (PFAE) dose-dependently inhibited systemic allergic reaction induced by compound 48/80 and anti-DNP IgE in rats (Shin *et al*., 2002). Allergic rhinitis and rhino conjunctivitis are characterized by an overreaction of the immune system. Ethanol extracts powder of *P. frutescens* (EPPF) and RA in mice models showed the protein levels and mRNA expressions of IL-1β, IL-6 and TNF-α were inhibited; histamine and IgE in the serum, spleen and nasal mucosa of OVA-sensitized mice were reduced by EPPF or RA administration. The mast cell and eosinophil infiltration increase by OVA-sensitization was decreased. It also inhibited both COX-2 protein expression and caspase-1 activity. The increased NF-κB/Rel A and caspase-1 activation in activated human mast cells was inhibited with the treatment of EPPF or RA (Oh *et al*., 2011). *P. frutescens* - derived methoxyflavanone (PDMF) significantly inhibits IgE-mediated histamine release from RBL-2H3 rat basophilic leukemia cells. Oral administration of PDMF not only suppresses passive cutaneous anaphylaxis, but also prevents allergic rhinitis-like nasal symptoms in a murine model of Japanese cedar pollinosis. Mechanistically, PDMF negatively regulates Akt phosphorylation and intracellular Ca2+ influx, both of which are essential for mast cell secretory granule translocation and its exocytosis upon high-affinity IgE receptor (FcεRI) cross-linking (Kamei *et al*., 2017). These results indicated that PLE and RA ameliorate allergic inflammatory reactions and potentially promising agents for the treatment of allergic diseases.

Anti-proliferative activity

P. frutescens has traditionally been used to treat diseases, including tumors. Studies evaluated the effects of PLE on proliferation and apoptosis in human hepatoma HepG2 cells indicated that the expression of apoptosis-

related genes were regulated in dose and time-dependent manner (Lin *et al*., 2007). Treatment of colorectal carcinoma cells (HCT116) and non-small cell lung carcinoma cells (H1299 cells) with PLE resulted in dose-dependent inhibition of growth by 52-92% (at the concentrations of 87.5, 175, and 350 µg/ml) and completely abolished the colony formation in soft agar at the concentration of 350 µg/ml. It resulted in change of the nucleus morphology and significantly increased sub-G1 cell population in both cells, indicating its apoptosis-inducing activity. PLE at the concentration range of 87.5 to 350 µg/ml was also effective in inhibiting the migration of H1299 cells by 52-58% and adhesion of both HCT116 and H1299 cells by 25-46% (Kwak and Ju, 2015). *P. frutescens* anthocyanins can induce HeLa cell apoptosis in a dose dependent manner (He *et al*., 2015). Triterpene acids (ursolic acid, corosolic acid and oleanolic acid) isolated from the ethanol PLE were found to be the active principles responsible for the cytotoxicity against three cultured human tumor cell lines - HL- 60 (leukemia carcinoma), MCF-7 (breast carcinoma), and Hep-G2 (hepatic carcinoma), with half maximal inhibitory concentration (IC_{50}) values of 12–48 µM (Akihisa *et al*., 2006) while isoegomaketone (IK) isolated from *P. frutescens* essential oils have been found to inhibits growth and apoptosis in melanoma cells via activation of ROS-mediated caspase-dependent and -independent pathways (Kwon *et al*., (2014). RA has been found to have anti-proliferative effect in *P. frutescens* decoction (IC_{50} @ 8.8 µg/ml) which significantly inhibited DNA synthesis of cultured murine mesangial cells induced by 1% fetal calf serum (Makino *et al*., 2001). *P. frutescens* oil and its active component- alpha-linolenic acid (ALA) have been reported to regulate the apoptosis-related protein expressions such as cleaved-poly ADP ribose polymerase (PARP), cleaved caspase-9 and -3, BCL-2 and BAX and exerted the protective activity from neuronal oxidative stress induced by H_2O_2 (Lee *et al*., 2018) and thus a promising agent against oxidative stress-induced apoptotic neuronal cell death. Zang *et al*., (2019) demonstrated PAH, another major oil components in *P. frutescens* increases AMPK phosphorylation and activity to induce gastric cancer cell autophagy to inhibit the growth of cultured mouse gastric cancer cell (MFCs) and human gastric cancer cell (GC9811-P) in time and concentration-dependent manner. *In-vivo* studies indicated that 4-week administration of PAH (100 mg/kg/day) suppressed the growth of gastric cancer and increased the levels of autophagy-related proteins, including beclin-1, LC3-II, cathepsin, caspase-3, p53, and cathepsin in tumors isolated from the xenograft model of gastric cancer in mice (Zhang *et al*., 2019). There is increasing research on active component inhibiting the growth of cancer cells. In perspective, therapy using the formulation containing active component of *P. frutescens* to treat cancer is likely the research area in future.

2. Conclusion

The present review highlighted the information about the various effects of *P. frutescens* and its benefits to health. Despite its numerous benefits and uses, this plant is still unknown to the common population. Therefore, there is a need to popularise the potential health benefits of this plant. At the same time, since the geographic region of origin greatly influenced the chemical composition and bioactivities of *P. frutescens*. It will be desirable to validate with more research work on the active component, dosage, toxicity etc., on its different parts of *P. frutescens* plant found in the region that could be used as an active constituent in the formulation of various functional foods or pharmaceuticals.

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