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Immunomodulatory effects of selected medicinal herbs and their essential oils: A comprehensive review

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ABSTRACT

Medicinal herbs and their essential oils are used in human health promotion and disease prevention since ancient times. In the last two decades, many studies have been carried out to both identify bioactive compounds in medicinal herbs and derived essential oils and to examine their biological effects in experimental models; clinical trials, however, have been scant. This review discusses *in vitro*, *in vivo*, and clinical evidence supporting the immunomodulatory role of eleven medicinal herbs (bay laurel, black cumin, clove, fennel, lemon balm, lemongrass, marjoram, peppermint, rosemary, sage, and thyme) and their essential oils and bioactive components. Safety and toxicity aspects for consumption as well as future perspectives are also covered. Relevant data from the existing literature have been compiled and summarized. These herbs and oils, which are increasingly consumed, can be considered as valuable dietary supplements due to their health-promoting bioactive constituents. Well-design clinical trials are warranted to better ascertain the immunomodulatory effects of these herbal products.

1. Introduction

Immunity has been a top health concern among consumers for the last decade. With the current coronavirus disease of 2019 (COVID-19) pandemic, interest in plant-based foods, beverages, dietary supplements, and herbal extracts, among others that may confer beneficial immunomodulatory effects, has grown dramatically. Given that immunocompromised individuals are prone to complications from COVID-19 infection and plant-based products have recently been reported to play important roles in enhancing immunity and helping control coronavirus infections (Arshad et al., 2020), plant-based immunity-enhancing compounds are in the limelight due to their potential health benefits. Strengthening of body's defense systems is one of the key factors that will both protect and lead to recovery in the event of COVID-19 infection (Babich et al., 2020). In addition, the immune system is a highly complex biological network that has evolved to protect the host from various pathogens, such as bacteria, viruses, parasites, and fungi, as well as cancer cells, while tolerating non-threatening organisms and nutrients (Lange & Nakamura, 2020; Parkin & Cohen, 2001). Supporting immunity through diet and/or herbal remedies can also have a positive impact on the gut microbiome, inflammation, viral infections, and nutritional imbalance, among others (Dong, Yu, Chen, & Wang, 2021).

The most popular medicinal herbs and their essential oils, possessing immunomodulatory properties, include bay laurel (*Laurus nobilis*), black cumin (*Nigella sativa*), clove (*Syzygium aromaticum*), fennel (*Foeniculum vulgare*), lemon balm (*Melissa officinalis*), lemongrass (*Cymbopogon citratus*), marjoram (*Origanum majorana*), peppermint (*Mentha piperita*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), and thyme (*Thymus vulgaris*) (Fig. 1).

Medicinal herbs and their essential oils are one of the richest sources of health-promoting bioactive compounds/phytochemicals (such as carotenoids, flavonoids, stilbenes, tannins, and omega-3 fatty acids, among others) (Chew & Park, 2004; González-Gallego, García-Mediavilla, Sánchez-Campos, & Tuñón, 2010; Gutiérrez, Svahn, & Johansson, 2019; Malaguarnera, 2019). Traditional medicinal herbs and derived oils have been used for centuries as medicines and/or dietary supplements for health promotion and treatment of a wide range of diseases. Some of these herbs are traditionally used as the accompanying

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treatments to medications aimed at boosting immunity (Babich et al., 2020). Presently, a myriad herbal products have been marketed, often with doubtful claims of improving immune health and reducing inflammation, and the demand for these products is rising globally.

While comprehensive reviews on the immune-mediated effects of vitamins, minerals, probiotics, and prebiotics are available in the literature, updated information is lacking on the immune effects of medicinal herbs, their essential oils, and the bioactive phytochemicals, mainly polyphenolic compounds, that they contain. Here, we summarize the evidence supporting the role of the common medicinal herbs listed in Fig. 1 and their essential oils in enhancing immunomodulatory effects. Safety and toxicity as well as future perspectives of these herbs and their essential oils are also discussed.

2. Methodologies

To write this review and to select the medicinal herbs and derived essential oils, we used the following methodologies. A detailed literature review was conducted within the TÜBİTAK-ULAKBIM (Turkish Academic Network and Information Center) database and various other data sources (such as Web of Science, PubMed, SCOPUS, MEDLINE, and Google Scholar) were screened to identify articles that fulfilled the following criteria: 1) medicinal herbs and derived essential oils showing immunomodulatory/anti-inflammatory effects, 2) research performed in animal (*in vivo*) studies, cell culture (*in vitro*) studies, molecular docking, and clinical trials, 3) study outcomes assessed specifically in relation to the immunomodulatory/anti-inflammatory effects, 4) description of the most effective extraction methods used, and 5) safety and toxicity of selected herb extracts and derived essential oils. We used the following search equation strategy and key-words (medicinal herbs, essential oils, immunomodulatory, immune-enhancing, anti-inflammatory, epidemiological, *in vivo* (animal and human) and *in vitro* studies, cell models, molecular docking, extraction, treatment, extract, safety, toxicology, and cytotoxicity, among others). Subject areas of "Pharmacology, Toxicology, and Pharmaceutics", "Agricultural and Biological Sciences", "Medicine", "Immunology and Microbiology", and "Multidisciplinary" were selected as inclusion criteria, whereas "Antioxidant", "Chemistry", "Engineering", "Nursing", "Materials Science", and "Environmental Science" were selected as exclusion criteria. To ensure that current and recent research was presented in this comprehensive review, only articles published from 2000 onward were included (with a few exceptions due to the relevance of the work), with preference given to articles published within 2015–2022 in order to improve contemporary relevance.

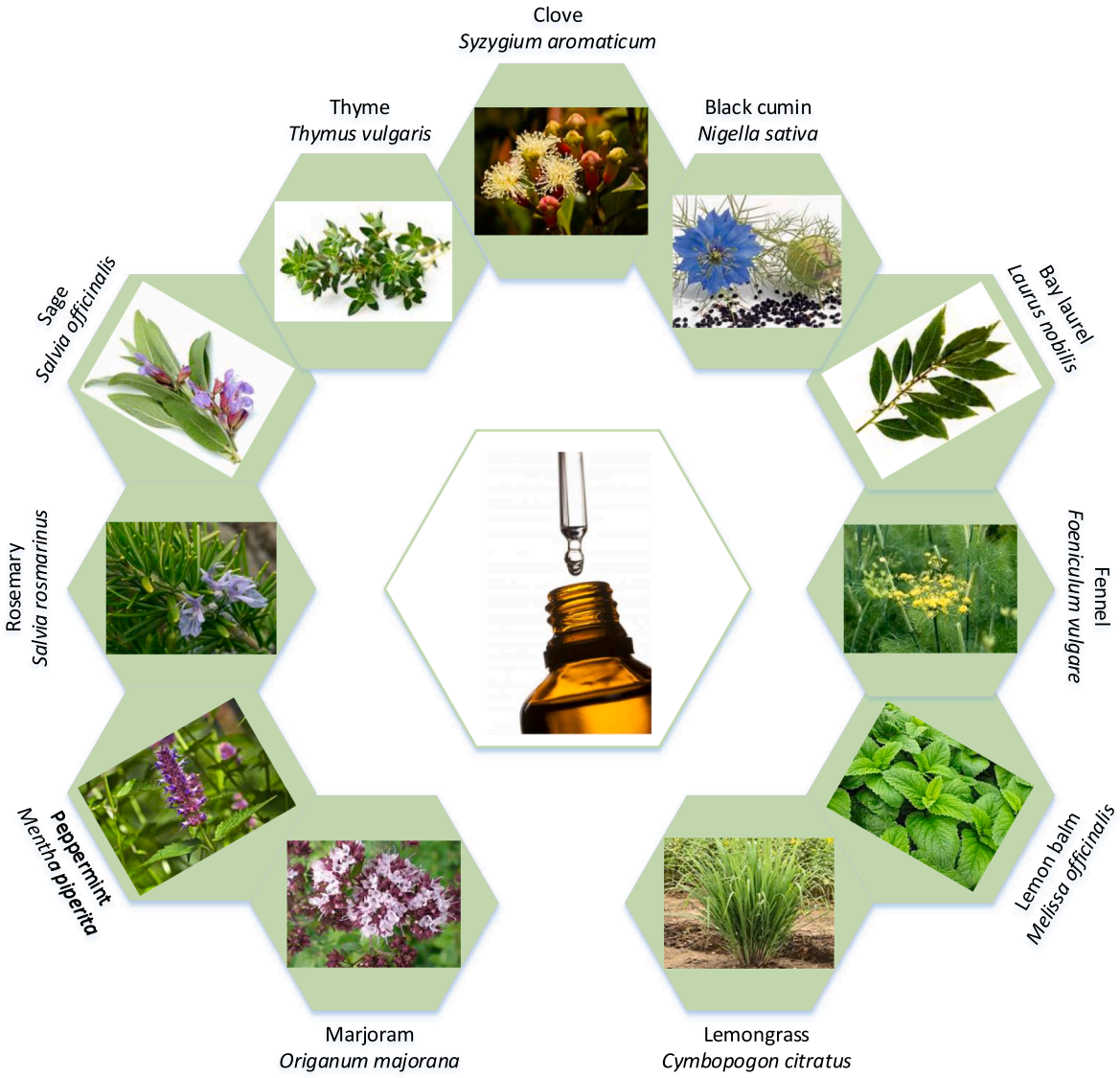

Fig. 1. Images of representative medicinal herbs.

Selected articles were examined in detail and then the immunomodulatory effects of selected herbs and derived oils determined in *in vitro* and *in vivo* studies (such as herbs, study design, cell or animal type, extraction method, treatment, and outcomes) were compiled. Finally, the safety and toxicity of selected herb extracts and their essential oils for consumption were evaluated. This review is not designed as a systematic review.

The most innovative aspect of this review is the selection of eleven medicinal herb extracts and derived essential oils from the most commonly used herbs, all of which exhibit immunomodulatory effects. In addition, detailed immunomodulatory effects of both extracts and derived essential oils determined by various studies and outcomes is another novelty of this study.

3. Immunomodulatory effects (epidemiological, *in vitro*, and *in vivo* studies) of selected herb extracts

Data from experimental studies on the immunomodulatory effects of eleven medicinal herbs are summarized in Table 1.

3.1. Bay laurel

Due to its reputed anti-inflammatory properties, bay laurel is commonly used as traditional medicine to treat joint and muscular pain. Mueller, Hobiger, and Jungbauer (2010) found that interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-α production, and cyclooxygenase-2 (COX-2) expression decreased upon treatment of lipopolysaccharide (LPS)-stimulated mouse macrophages with bay laurel extract. All these effects are anti-inflammatory except for the reduction of IL-10, a cytokine that is a strong suppressor of inflammatory responses. Lee, Shin, Kim, Lee, Yang, and Seo (2019) used both *in vitro* and *in vivo* models to evaluate the anti-inflammatory effects of bay laurel extract. Results of cell culture studies in mouse bone marrow progenitor cells showed that bay laurel reduced the expression of inflammatory cytokines IL-1β, IL-6, and TNF-α, while in a murine model of lung injury the laurel extract reduced inflammasome activation. In addition, Guedouari and Nabiev (2021) showed that ethanolic extract (26%) and fixed oil of laurel fruit reduced experimental paw edema in a BALB/c male mice model. The available evidence points to an anti-inflammatory effect of bay laurel.

3.2. Black cumin

Black cumin is an herb native to the Middle East which seeds have long been used as culinary spice and in traditional medicine for various purposes. Studies have reported the therapeutic effects of black cumin and its major components thymoquinone (TQ) and α-hederin. In *in vitro* studies with various LPS-stimulated macrophage-like cell models, TQ suppressed nitric oxide (NO) production and IL-6, IL-1β, TNF-α, inducible nitric oxide synthase (iNOS), and COX-2 expression; reduced the nuclear levels of transcription factors and the phosphorylation patterns of signaling proteins, the activator protein-1 (AP-1) and nuclear factor-kappa B (NF-κB) pathways; and suppressed IL-1 receptor-associated kinase 1-linked AP-1/NF-κB and AP-1/NF-κB signaling pathways (Hossen, Yang, Kim, Aravinthan, Kim, & Cho, 2017). In *in vivo* studies, the same authors (Hossen et al., 2017) demonstrated strong anti-inflammatory effects of oral TQ in murine models of experimental gastritis and hepatitis. In a rodent model, Ammar, Gameil, Shawky, and Nader (2011) showed that oral TQ had inhibitory effects on iNOS and transforming growth factor-beta (TGF-β1), reduced inflammation induced by experimental asthma, and decreased serum immunoglobulin E level. Similar to TQ, α-hederin also interfered with miRNA-126 expression, disrupted the IL-13 secretory pathway, and induced anti-inflammatory effects in sensitized rats (Fallahi, Keyhanmanesh, Khamaneh, Saadatlou, Saadat, & Ebrahimi, 2016). Recently, Bouchentouf and Missoum (2020) used molecular docking studies to show that black cumin and its essential oils inhibited COVID-19 and severe acute respiratory syndrome (SARS) virus. The results of the main protease investigation for COVID-19 suppression showed that black cumin was equal or superior to Food and Drug Administration (FDA)-approved drugs in terms of anti-inflammatory and antiviral effects. In conclusion, black cumin appears to be a potent anti-inflammatory and immunomodulatory agent.

3.3. Clove

Clove is widely used as a spice for food flavoring. Recent studies have analyzed the medicinal properties of clove and its main constituents, eugenol and isoeugenol. In an *in vitro* study using LPS-stimulated mouse macrophages by Bachiega, de Sousa, Bastos, and Sforcin (2012), both extracts of clove and eugenol at low doses increased IL-1β, IL-6, and IL-10 production, while high doses decreased production of these cytokines. Pérez-Rosés, Risco, Vila, Peñalver, and Cañigueral (2015) assessed *in vitro* the immunomodulatory effects of different dilutions of pure eugenol and showed a modest 29% inhibition of phagocytosis in human neutrophils at 57.6 μg/mL and inactivation of the classical pathway of complement with a moderate the half-maximal inhibitory concentration (IC_{50}) value of 78.3 μg/mL, without effect on the alternate pathway of complement. Dibazar, Fateh, and Daneshmandi (2015) reported the restricted immunomodulatory effect of a clove extract in an *in vitro* study using mouse peritoneal macrophages. Cytokine formation/release was mainly dose-dependent and biphasic for IL-6 and TNF-α, there was suppression of NO and TNF-α production, inconsistent effects on IL-12, and enhanced IL-6 production. Using the same cell culture model of LPS-activated mouse macrophages used for bay laurel, Mueller et al. (2010) found that IL-6 production was reduced with 0.2 and 0.5 mg/mL of clove extract, but there was no effect on IL-10 or TNF-α expression. Furthermore, COX-2 expression also slightly declined with clove extract, while iNOS expression was unaffected. Rodrigues, Fernandes, Sousa, Bastos, and Sforcin (2009) conducted an *in vivo* study in BALB/c mice, from which peritoneal macrophages were obtained *via* phosphate-buffered saline inoculation after oral administration of an aqueous clove extract (200 mg/kg body weight for 3 days). Results showed a strong inhibition of production of IL-1β and IL-6 by LPS-activated macrophages. In conclusion, the available evidence suggests that clove possesses immunomodulatory effects.

3.4. Fennel

Various parts of fennel are used in traditional medicine, particularly as diuretics and to treat inflammatory conditions and infections. Cherng, Chiang, and Chiang (2008) reported that an aqueous extract of fennel's root did not stimulate the proliferation of human peripheral blood mononuclear cells and/or the secretion of interferon-gamma (IFN-γ), whereas aqueous extracts of fennel's aerial parts did stimulate proliferation. On the other hand, Darzi, Khazraei, and Amirghofran (2018) showed that an alcoholic extract of fennel's aerial parts at a concentration of 100 μg/mL decreased IL-4 and IFN-γ secretion from activated human lymphocytes without affecting cell viability. The extract of fennel leaves collected in winter was the most active to inhibit the expression of the COX-2 gene in a human monocytic cell line (THP-1 macrophages), among other seasonal extracts (Pacifico et al., 2018). Thus, limited evidence suggests an immunomodulatory effect of fennel.

3.5. Lemon balm

Lemon balm is a perennial aromatic herb that has been used for centuries in the treatment of pain and inflammation and as a memory stimulant. Several animal studies have been performed to evaluate its anti-inflammatory activity. Drozd and Anuszewska (2003) tested the immunomodulatory activity of lemon balm in mice immunized with sheep red blood cells. Depending on the route of oral or subcutaneous administration, lemon balm enhanced the ability to associate with ram red blood cells in the E rosette formation test; however, titers of

Table 1
The immunomodulatory effects of selected herbs determined by *in vitro* and *in vivo* studies.

Herbs	Study design	Cell or animal type	Extraction method	Treatment	Outcomes*	Author (year)
Bay laurel	*in vitro* (cell culture)	Mouse macrophages (RAW 264.7) stimulated with LPS (1 μg/mL)	Maceration (DMSO)	0.2 and 0.5 mg/mL of extract	↓ IL-6, IL-10, and TNF-α production ↓ COX-2 expression ↔ iNOS expression	Mueller et al. (2010)
		Bone marrow progenitor cells from C57BL/6 mice	Maceration (ethanol)	25 and 50 μg/mL of ethanolic extract	↓ IL-1β, IL-6, and TNF-α expression	Lee et al. (2019)
	in vivo (animal)	Mice with acute lung injury induced by intratracheal LPS administration	Maceration (ethanol)	i.p. injection of 30 mg/kg ethanolic extract	↓ NLRP3 inflammasome activation	Lee et al. (2019)
		BALB/c male mice with paw edema induced by carrageenan injection under the plantar aponeurosis	Maceration (ethanol)	Injection of 100 mg/kg ethanolic extract under the plantar aponeurosis	↓ Paw volume with a percentage inhibition of 26.3%	Guedouari and Nabiev (2021)
Black cumin	*in vitro* (cell culture)	Mouse macrophages (RAW264.7), human monocytes (U937), and HEK293 cells stimulated with LPS (1 μg/mL)	Commercial product	TQ 6.25–25 μM	↓ NO production ↓ IL-1β, IL-6, TNF-α, iNOS, and COX-2, expression ↓ IRAK-linked AP-1/NF-κB pathways	Hossen et al. (2017)
	in vivo (animal)	Swiss albino mice with ovalbumin and ovalbumin-TQ treated groups	Commercial product	Oral TQ at 10 mg/kg/day	↓ Serum IgE ↓ iNOS ↓ TGF-β1 ↓ Inflammatory changes associated to asthma	Ammar et al. (2011)
		Wistar rats	Commercial product	TQ 3 mg/kg and α-hederin 0.02 mg/kg by i.p. injection	↓ miRNA-126 ↓ IL-13 mRNA ↓ Inflammatory responses ↑ α-Hederin and TQ asthma prevention	Fallahi et al. (2016)
		Male C57BL/6 and ICR mice with HCl/EtOH-induced gastritis and LPS/D-GalN-induced hepatitis treated with LPS (10 μg/kg) and D-GalN (1 g/kg), i.p. injection	Commercial product	TQ 5 and 25 mg/kg, orally	In gastritis model (TQ 5 and 25 mg/kg): ↓ Histopathological gastritis and leukocyte infiltration In hepatitis model (TQ 25 mg/kg): ↓ Serum aminotransferases ↓ Hepatic leukocyte infiltration	Hossen et al. (2017)
	Molecular docking	na	Commercial product &maceration (hexane)	na	↑ Inhibition of COVID-19 and SARS virus by acting on the main protease M^{pro} ↑ 6LU7 active site docking with energy score − 6.29734373 kCal/mol by nigelledine ↑ 2GTB active site docking with energy score − 6.50204802 kcal/mol by α-hederin	Bouchentouf and Missoum (2020)
Clove	*in vitro* (cell culture)	Mouse peritoneal macrophages incubated with LPS (5 μg/mL)	Maceration (methanol: water)	Incubation with clove or eugenol at 5, 10, 25, 50, or 100 mg/well	↑ IL-1β, IL-6, and IL-10 production at low doses ↓ IL-1β, IL-6, and IL-10 production at high doses	Bachiega et al. (2012)
		Human neutrophils (flow cytometry) and complement activation (hemolytic assay)	Commercial product	Eugenol at different dilutions in Hanks' balanced salt solution with 10% DMSO	↑ Inhibition of phagocytosis at 57.6 μg/mL ↑ Inhibition of classical complement pathway activation (IC_{50} 78 μg/mL) ↔ Inhibition of alternate complement pathway activation	Pérez-Rosés et al. (2015)
		Peritoneal macrophages isolated from healthy naïve BALB/c mice Stimulated with RPMI medium alone or containing 10 μg/mL LPS	Maceration (water or ethanol)	Clove extracts at concentrations of 0.001–1.0 mg/mL	↓ NO production ↑ Dose-related and seemingly bi-phasic macrophage cytokine formation/release (for IL-6 and TNF-α) ↔ IL-12 production ↓ NO and TNF-α production ↑ IL-6 production	Dibazar et al. (2015)
		Mouse macrophages (RAW 264.7) stimulated with LPS (1 μg/mL)	Maceration (DMSO)	0.2 and 0.5 mg/mL of extract	↓ IL-6 production ↓ COX-2 expression	Mueller et al. (2010)

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Table 1 (*continued*)

Herbs	Study design	Cell or animal type	Extraction method	Treatment	Outcomes*	Author (year)
					↔ IL-10 and TNF-α production ↔ iNOS expression	
	in vivo (animal)	Male BALB/c mice. Peritoneal macrophages obtained from abdominal cavity, LPS-activated (5 μg/mL)	Maceration (ethanol: water)	Aqueous clove extract, 200 mg/kg bw orally for 3 days	↓ IL-1β and IL-6 production by macrophages from clove-treated mice	Rodrigues et al. (2009)
Fennel	*in vitro* (cell culture)	Mononuclear cells from healthy volunteers	Aqueous extract of aerial parts	0.05 mL of test sample mixed with PBMC	↑ Proliferation of human PBMC and secretion of IFN-γ	Cherng et al. (2008)
		Human peripheral blood lymphocytes activated by phytohemagglutinin	Butanol extract of aerial parts	100 μg/mL extract	↓ IL-4 and IFN-γ secretion	Darzi et al. (2018)
		Human leukemic monocytic cell line THP-1 stimulated with LPS, 7.5 ng/mL	UAE (methanol:water)	50 μg/mL extract	↓ COX-2 gene expression (winter extract inhibitory but spring extract weakly stimulatory)	Pacifico et al. (2018)
Lemon balm	*in vivo* (animal)	Female BALB/c mice immunized with sheep red blood cells	Maceration (water)	E rosette formation test (orally and subcutaneously): 10 X diluted (186 ± 35) Hemagglutination test (orally and subcutaneously) : 10 X diluted (100 ± 0.0)	↑ Splenocyte ability to associate with ram red blood cells in E rosette formation test ↔ Titers of antibodies against sheep red blood cells in hemagglutination test	Drozd and Anuszewska (2003)
		Male albino Sprague-Dawley rats and mice with histamine-induced paw edema	Maceration (water)	400 mg/kg of extract injected subcutaneously into the paw plantar surface	↓ Inflammagen induced paw edema in rats ↓ Nociceptive response in mice	Birdane et al. (2007)
		Male Wistar albino rats with doxorubicin-induced cardiotoxicity	Maceration (70% ethanol)	750 mg/kg bw of extract for 10 days by oral gavage	In heart tissue: ↓ Expression of NF-κB, TNF-α, and COX-2 ↓ Myeloperoxidase levels	Hamza et al. (2016)
Lemongrass	*in vitro* (cell culture)	Murine alveolar macrophages from BALB/c mice, LPS-stimulated (1 μg/mL)	Maceration (ethanol:water)	5 and 10 μg of extract	↓ Release of pro-inflammatory mediators TNF-α and NO	Tiwari et al. (2010)
		Peritoneal macrophages from BALB/c mice, LPS-stimulated (5 μg/mL)	Maceration (methanol:water)	Lemongrass and citral at 5, 10, 25, 50, and 100 μg/well	↑ IL-1β production by lemon grass at 5 and 10 μg/well, no effect at bigger doses ↓ IL-1β production by citral at 50 and 100 μg/well ↓ IL-6 production by lemon grass at 100 μg/well and citral at all doses ↓ IL-10 production	Bachiega and Sforcin (2011)
		Human and murine macrophages (RAW264.7), LPS-stimulated (1 μg/mL)	Water, methanol, and ethanol fractions by column chromatography	Incubation with 1.115 mg/mL extract, 530 μg/mL phenolic acid-rich fraction, 97.5 μg/mL flavonoid-rich fraction, and 78 μg/mL tannin-rich fraction	↓ NF-κB activation ↓ TNF-α and CCL5 expression ↓ Proteasome activity, a complex that controls NF-κB activation, chlorogenic acid having a strong contribution	Francisco et al. (2013)
	in vivo (animal)	BALB/c mice treated with lemongrass with harvesting ofperitoneal macrophages, stimulated with LPS (5 μg/mL)	Maceration (methanol:water)	200 mg/kg bw for 3 days by oral gavage	↓ IL-1β production ↑ IL-6 production	Sforcin et al. (2009)
		Wistar albino rats with adenine-induced chronic kidney disease	Commercial product	360 mg/kg daily for 4 weeks, orally	In renal tissue: ↓ TNF-α and endothelin-1 expression ↑ IL-10 and VEGF expression	Said et al. (2019)
Marjoram	*in vitro* (cell culture)	Human THP-1 monocytes stimulated with LPS (0.05 μg/mL)	Pressurized liquid extraction (ethanol: water)	Original extract and rosmarinic acid-enriched extract	↓ TNF-α, IL-1β, and IL-6 secretion	Villalva et al. (2018)
		Human THP-1 monocytes (incubation with LPS (0.05 μg/mL)	Pressurized liquid extraction and ultrasound-assisted extraction (ethanol:water)	0.5 and 1 mg/mL of extract	↓ TNF-α, pro- IL-1β, and IL-6 secretion	Arranz et al. (2019)

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Table 1 (*continued*)

Herbs	Study design	Cell or animal type	Extraction method	Treatment	Outcomes*	Author (year)
	in vivo (animal)	Male albino rats with myocardial toxicity induced by doxorubicin	Maceration (methanol:water)	750 mg/kg for 24 days, orally	↓ Serum IL-6 and TNF-α levels	Mansoury (2019)
		Wistar rats with dehydro-epiandrosterone induced-polycystic ovary syndrome	Commercial product	20 mg/kg, for 3 weeks, orally (by gavage)	↓ IL-6 and TNF-α levels in ovary tissues	Rababa'h et al. (2020)
Peppermint	*in vitro* (cell culture)	Murine macrophage cell line RAW 264.7 Human larynx epidermal carcinoma (Hep-2) cell line, stimulated with LPS (1 μg/mL)	Hot extraction (ethanol)	Extract at 5, 10, 50, 100, and 200 μg/mL	↓ NO production ↓ IL-6, TNF-α, and PGE2 production ↑ Antioxidant activity (with synergistic action of extract constituents) ↑ Effect against respiratory syncytial virus	Li et al. (2017)
	in vivo (animal)	Female BALB/c mice infected with *S. mansoni cercariae*, BH strain	Commercial product	Drug composed of menthol (30–55%) and menthone (14–32%) prepared from leaves (50 mg/kg/0.2 mL/day) administered by gavage	Antiparasitic effect: ↓ Mononuclear and eosinophile blood cell counts ↓ IL-4 and IL-10 plasma levels	Zaia et al. (2016)
		Male albino Wistar rats with acetic acid-induced colitis	Commercial product	Menthol, 50 mg/kg orally 3 days pre- or 7 days post-induction of colitis	↓ Macro and microscopic colonic inflammation In colon homogenate: ↓ MPO activity ↓ Calprotectin levels ↓ IL-1β, IL-23, and TNFα levels ↔ IL-6 levels	Bastaki et al. (2018)
		Male Wistar rats fed oxidized palm oil	Maceration (water)	500 mg/kg bw/day of peppermint extract by oral gavage for 6 weeks	Partial reversion of abnormalities induced by oxidized palm oil: ↑ Serum IgG, IgM, and IgA ↓ CRP, IL-1, IL-6, TNF-α, and MCP-1	Osman et al. (2020)
Rosemary	*in vitro* (cell culture)	Human THP-1 macrophages treated with basolateral fractions of CaCO-2 cells exposed to rosemary extract	Supercritical extraction	20 μg/mL extract	↓ TNF-α, IL-1β, IL-6, and IL-10 excretion	Arranz et al. (2015a)
		Splenocytes from BALB/C mice stimulated with mitogens (LPS and concanavalin A)	Supercritical extraction	Rosemary emulsions digested in CaCO-2 cell and HT-29 MTX mixed cell cultures	↓ Proliferation of activated murine splenocytes	Arranz et al. (2017)
		RAW 264.7 murine macrophages stimulated with LPS (1 μg/mL)	Maceration (methanol, n-hexane, and ethyl acetate)	1.25–10 μg/mL ethyl acetate and 12.5–100 μg/mL n-hexane	↓ LPS-induced NO and PGE2 production with n-hexane	Karadağ et al. 2019
		RAW 264.7 murinemacrophages stimulated with LPS (1 μg/mL)	Maceration (DMSO)	Rosemary extract at 0.2 and 0.5 mg/mL Rosmarinic acid at 50 and 100 nM	↓ IL-6 and IL10 production by rosemary ↑ IL-10 production by rosmarinic acid ↓ iNOS by rosmarinic acid	Mueller et al. (2010)
		Bone marrow mast cells from C57BL/6 mice IL-3 and PGE2-conditioned andsubsequently stimulated with TNP-BSA plus SCF (both at 100 ng/mL)	Maceration (dichloromethane-methanol)	100 mg/mL of extract and 100 mM standards	↓ p38 and JNK MAPKs phosphorylation ↓ NF-κB transcription factor activity. ↓ IL-6, IL-13, TNF-α, CCL1, and CCL3 secretion	Yousef et al. (2020)
	in vivo (animal)	Swiss mice with pleurisy induced by intrapleural injection of carrageenan	Maceration (hexane, ethyl acetate, and ethanol)	Extracts given by i.p. injection 0.5 h prior to pleurisy induction	↓ Leukocyte exudation ↓ IL-1β and TNF-α levels, myeloperoxidase activity and nitrite/nitrate concentrations in pleural exudate	Benincá et al. (2011)
		Adult male Wistar rats with painful neuropathy induced by chronic constriction of the sciatic nerve	Maceration (ethanol)	Ethanolic extract, 400 mg/kg, and rosmarinic acid, 40 mg/kg, *via* intra- peritoneal injection for 14 days	↓ COX-2, PGE2, IL-1β, matrix metalloproteinase-2, and NO expression in lumbar spine	Rahbardar et al. (2017)
Sage	*in vitro* (cell culture)	RAW264.7 murine macrophages stimulated with LPS (1 μg/mL)	Reflux with ethanol and fractionation with water, hexane, dichloromethane, and ethyl acetate	Isolates of extract	↓ iNOS and COX-2 expression ↓ JNK phosphorylation in the MAPK signaling pathway	Li et al. (2019)
		RAW264.7 murinemacrophages stimulated with LPS (1 μg/mL)	Maceration (DMSO)	0.2 and 0.5 mg/mL of extract	↓ IL-6, IL-10, and TNF-α secretion ↓ iNOS expression	Mueller et al. (2010)

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Table 1 (*continued*)

Herbs	Study design	Cell or animal type	Extraction method	Treatment	Outcomes*	Author (year)
					↔ COX-2 expression	
		RAW 264.7 murine macrophages stimulated with LPS (1 μg/mL)	Maceration and UAE (methanol)	na	↓ NO production *via* NF-κB inhibition ↓ IL-1β, IL-6, and TNF-α expression ↓ ROS formation	Brindisi et. al (2021)
		Neuroblastoma cells (SK-N-SH) and human subcutaneous mature adipocytes	Commercial product (ethanolic extract)	Sage extract, 5 μg/mL and 50 μg/mL, with or without 0.5 ng/mL of human recombinant IL-1β	↓ MCP-1, IL-6, IL-8, and TNF-α basal levels in adipocytes for acute and chronic treatments ↓ ACM effect on IL-6, IL-8, and VCAM-1	Russo et al. (2021)
	in vivo (animal)	C57Bl6 mice with diet-induced obesity	Soxhlet (methanol)	100 and 400 mg/kg/day bid methanol extract orally for 5 weeks	↑ Plasma levels of IL-2, IL-4, and IL-10 ↓ Plasma levels of IL-12, TNF-α, and KC/GRO	Ben Khedher et al. (2018)
Thyme	*in vitro* (cell culture)	J774A.1 murine macrophages stimulated with LPS and IFN-γ	Commercial product	8.5, 16, 50.4 and 84 μg/mL of thyme extract	↓ NO production in a dose-dependent manner ↓ iNOS mRNA expression at 84 μg/mL of extract	Vigo et al. (2004)
		RAW 264.7 murinemacrophages stimulated with LPS (1 μg/mL)	Maceration (DMSO)	0.5 mg/mL of extract	↓ IL-6, IL-10, and TNF-α secretion ↓ iNOS expression strongly ↔ COX-2 expression	Mueller et al. (2010)
		Mitogen-induced peripheral blood lymphocytes and Jurkat cell line	Maceration (methanol)	50 and 200 μg/mL	↓ Lymphocyte proliferation	Amirghofran et al. (2011)
		RAW 264.7 murine macrophages stimulated with LPS (1 μg/mL)	Commercial product	25, 50, and 100 mg/mL extract	↓ IL-1β and TNF-α production in a dose-dependent manner	De Oliveira et al. (2017)
	in vivo (animal)	Male Wistar rats fed oxidized palm oil	Maceration (water)	500 mg/kg bw/day of thyme extract by oral gavage for 6 weeks	Partial reversion of abnormalities induced by oxidized palm oil: ↑ Serum IgG, IgM, and IgA ↓ CRP, IL-1, IL-6, TNF-α, and MCP-1	Osman et al. (2020)

Abbreviations: ACM, adipocytes conditioned media; AP-1, activator protein-1; bw, body weight; BH, Benjamini-Hochberg; bid, bis in die (twice a day); CCL, C-C motif chemokine ligand; COVID-19, coronavirus disease of 2019; COX-2, cyclooxygenase-2; CRP, C-reactive protein; D-GalN, D-galactosamine; DMSO, dimethyl sulfoxide; EtOH, ethanol; GTB, glycosyltransferases B; HCl, hydrochloric acid; IC_{50}, the half-maximal inhibitory concentration; IFN-γ, interferon-gamma; IgA, Immunoglobulin A; IgE, Immunoglobulin E; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IL, interleukin; iNOS, inducible nitric oxide synthase; i.p., intraperitoneal: IRAK, interleukin-1 receptor-associated kinase 1; JNK, c-Jun N-terminal kinase; KC/GRO, keratinocyte-derived chemoattractant/human growth-regulated oncogene; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; miRNA, micro ribonucleic acid; mRNA, messenger ribonucleic acid; MPO, myeloperoxidase; na, not available; NF-κB, nuclear factor-kappa B; NLRP3, NOD-like receptor pyrin domain-containing 3; NO, nitric oxide; PBMC, peripheral blood mononuclear cells; PGE2, prostaglandin E-2; ROS, reactive oxygen species; RPMI, Roswell Park Memorial Institute; SARS, severe acute respiratory syndrome; SCF, stem cell factor; TGF-β1, transforming growth factor-beta 1; THP-1, Tohoku Hospital Pediatrics-1; TNF-α, tumor necrosis factor alpha; TNP-BSA, 2,4,6-trinitrophenyl bovine serum albumin; TQ, thymoquinone; UAE, ultrasound-assisted extraction; VCAM-1, vascular cell adhesion molecule-1, VEGF, vascular endothelial growth factor.

* Results: ↑, ↓, and ↔ present significant increase, significant decrease, and non-significant effect, respectively.

antibodies against sheep red blood cells were unchanged in a hemagglutination test. Also, Birdane, Büyükokuroglu, Birdane, Cemek, and Yavuz (2007) examined the anti-inflammatory activity of lemon balm in a rat model of histamine-induced and carrageenan-induced paw edema. Besides reduction of paw edema and of the nociceptive response, results showed that lemon balm inhibited the formation of several inflammation mediators. In other *in vivo* experiments, Hamza, Ahmed, Elwey, and Amin (2016) used a model of doxorubicin-induced cardiotoxicity in male Wistar albino rats. Besides other cardioprotective effects, oral pretreatment with 750 mg/kg lemon balm extract significantly down regulated the expression of NF-κB and its downstream inflammatory mediators TNF-α and COX-2 in heart tissue, while reducing myeloperoxidase levels, which attests to a clear anti-inflammatory effect. Hence, lemon balm appears to be useful as an anti-inflammatory agent.

3.6. Lemongrass

Lemongrass has been widely used in traditional medicine for the treatment of inflammatory disorders; its anti-inflammatory potential has been evaluated in several experimental studies. The effect of lemongrass on cytokine expression in *in vitro* studies using LPS-stimulated macrophages has been investigated by several authors (Bachiega & Sforcin, 2011; Francisco et al., 2013; Tiwari, Dwivedi, & Kakkar, 2010). Results of these studies showed a reduction in the release of pro-inflammatory mediators such as TNF-α and NO by murine alveolar macrophages (Tiwari et al., 2010), variable effects depending on dose of lemongrass and its major constituent citral on IL-1β and IL-6 production, with reduced secretion of the anti-inflammatory cytokine IL-10 in mouse peritoneal macrophages (Bachiega & Sforcin, 2011), and decrease in cytokine production through the NF-κB pathway in human and mouse macrophages by extracts of lemongrass and its main polyphenols, with a major contribution of chlorogenic acid (Francisco et al., 2013). The *in vivo* activity of lemongrass on pro-inflammatory cytokine production was searched by Sforcin, Amaral, Fernandes, Sousa, and Bastos (2009), who observed a significant inhibition of IL-1β production but increased IL-6 production in mice peritoneal macrophages harvested after the oral administration of an aqueous extract of lemongrass, 200 mg/kg for 3 days. However, as discussed in the next section, incubation of

macrophages with lemongrass essential oil led to a decreased production of both IL-1β and IL-6. The anti-inflammatory effects of lemongrass were also investigated in a rat model of chronic kidney disease induced by adenine (Said, Atwa, & Khalifa, 2019). Results demonstrated that oral treatment with lemongrass mitigated the harmful renal effects of adenine, downregulated TNF-α and endothelin-1 expression, and increased the expression of the anti-inflammatory cytokine IL-10 and vascular endothelial growth factor. In summary, there is fair experimental evidence supporting the anti-inflammatory effects of lemongrass.

3.7. Marjoram

Marjoram, which is generally consumed as spice or flavor, has a wide range of biological activities, with antioxidant, antimicrobial, anti-inflammatory, and hepatoprotective effects among others. The anti-inflammatory effects of marjoram and its major active component, the polyphenolic molecule rosmarinic acid, were investigated in two studies from the same investigators (Arranz et al., 2019; Villalva, Jaime, Aguado, Nieto, Reglero, & Santoyo, 2018) in a human THP-1 macrophage model; the results showed significant decreases in macrophage TNF-α, IL-1β, and IL-6 secretion. In addition, Mansoury (2019) investigated the immunomodulatory properties of oral treatment with marjoram *via* assessing anti-inflammatory cytokines in a murine model of myocardial toxicity induced by doxorubicin and showed significant decreases in serum TNF-α and IL-6 levels, besides other protective effects against doxorubicin cardiac toxicity. The anti-inflammatory effect of marjoram extract was recently investigated in rats with polycystic ovary syndrome (Rababa'h, Matani, & Ababneh, 2020). In this study, treatment with both oral marjoram alone and a marjoram-metformin combination resulted in significantly decreased IL-6 and TNF-α levels in ovary tissue. Thus, experimental evidence points to marjoram as a relevant anti-inflammatory agent.

3.8. Peppermint

Mentha piperita is a common mint species known for its flavoring and medicinal properties, used in food, cosmetics, and herbal medicines. Peppermint and its main constituents (menthol and menthone) have been investigated for immunological and anti-inflammatory effects. Li, Liu, Ma, Bao, Wang, and Sun (2017) studied the effects of an ethanol extract of peppermint in an *in vitro* assay in a murine macrophage cell line and showed decreased production of NO, TNF-α, IL-6, and prostaglandin E-2 (PGE-2). In the assay, the LPS-induced NO production decreased in a concentration-dependent manner. In an *in vivo* study in mice infected with *Schistosoma mansoni*, Zaia et al. (2016) evaluated the immunological effects of prolonged oral administration of a commercial peppermint product consisting of menthol (30–-55%) and menthone (14–32%). The results showed an antiparasitic effect of peppermint together with a reduced immune Th2-type 2 response and increased IL-10 anti-inflammatory cytokine expression. However, a decrease in IL-4 and IL-10 blood levels was also observed. Bastaki, Adeghate, Amir, Ojha, and Oz (2018) used an *in vivo* murine model of experimental colitis to assess the anti-inflammatory effects of menthol. Oral administration of menthol at 50 mg/kg before or after induction of colitis with intrarectal acetic acid prevented or mitigated colonic inflammation and significantly reduced the levels of myeloperoxidase and calprotectin (a protein released by neutrophils in inflammatory bowel conditions) in colonic tissue, as well as those of pro-inflammatory cytokines IL-1, IL-23, and TNF-α, but not IL-6. Recently, Osman, Alsharari, and Alsufiani (2020) demonstrated that an oral peppermint extract partially reverted the immune and inflammatory response to oxidized palm oil feeding in male Wistar rats. Results showed increased serum immunoglobulin G, immunoglobulin M, and immunoglobulin A and reduced C-reactive protein (CRP), IL-1, IL-6, TNF-α, and monocyte chemoattractant protein-1 (MCP-1) levels. In conclusion, *Mentha piperita* discloses immunomodulatory properties in experimental models, but further studies are warranted.

3.9. Rosemary

Rosemary is a perennial shrub native to the Mediterranean area. While its leaves are commonly used in food seasoning and as antioxidant for food conservation, this highly aromatic herb is also reputed for its analgesic and anti-inflammatory effects and has long been used in folk medicine. Arranz et al. (2015a) examined the anti-inflammatory activity of the basolateral fraction of CaCO-2 cells exposed to rosemary supercritical extract on human THP-1 macrophages and demonstrated reduced TNF-α, IL-1β, IL-6, and IL-10 excretion. The anti-inflammatory activity was mainly due to carnosic acid and carnosol. In a subsequent study, Arranz, Guri, Fornari, Mendiola, Reglero, and Corredig (2017) tested the effect of rosemary supercritical fluid extract on the proliferation of activated murine splenocytes and showed an inhibitory effect consistent with improved immune regulation. The *in vitro* antioxidant, antibacterial, cytotoxic, anti-inflammatory, and analgesic activities of non-polar and polar fractions of rosemary flowers were evaluated by Karadağ et al. (2019) in LPS-stimulated murine macrophages. Results disclosed decreased NO and PGE-2 production by the n-hexane fraction of rosemary flowers. Mueller et al. (2010) assessed the anti-inflammatory activity of both rosemary extract and rosmarinic acid and reported that the latter at concentrations of 50 and 100 nM reduced IL-6 secretion and increased anti-inflammatory IL-10 secretion; conversely, rosemary plant extract reduced IL-10 secretion, although it decreased the expression of iNOS. Yousef et al. (2020) evaluated the potential of rosemary extract in modulating murine bone marrow mast cell activation and FcεRI/c-kit signaling, potentially *via* mitogen-activated protein kinases (MAPK) and NF-κB pathways. Gene expression and mediator secretion analysis showed that rosemary extract treatment inhibited early phase mast cell degranulation (down to 15% of control) and decreased IL-6, TNF, IL-13, C-C motif chemokine ligand 1, and C-C motif chemokine ligand 3 secretion. With this study, authors demonstrated the potential of rosemary as a novel therapeutic agent for the treatment of allergically activated mast cells.

The anti-inflammatory effects of rosemary and its components were also examined in *in vivo* models. Benincá, Dalmarco, Pizzolatti, and Fröde (2011) studied crude rosemary extract, its derived fractions of hexane, ethyl acetate, and ethanol as well as its isolated components (carnosol, betulinic acid, and ursolic acid) in a mouse pleurisy model. The tested compounds reduced pleural exudate leukocyte numbers, myeloperoxidase activity, and NO concentration. A significant decrease in pleural exudate levels of IL-β and TNF-α was also observed. Rahbardar, Amin, Mehric, Mirnajafi-Zadeha, and Hosseinzadeh (2017) investigated the effect of rosemary extract and rosmarinic acid on the lumbar spinal cord expression of inflammatory and oxidative stress markers in a murine model of neuropathic pain induced by sciatic nerve constriction. After injury, significant increases in COX-2, PGE-2, IL-β, matrix metalloproteinase-2, and NO were observed in lumbar spinal cord tissue, which were reverted by intraperitoneal administration of both rosemary extract and rosmarinic acid. In summary, there is consistent experimental evidence for the immunomodulatory activity of rosemary and its main constituents.

3.10. Sage

Sage is an aromatic plant cultivated worldwide, especially in the Mediterranean region, well-known for its various health-promoting properties. The anti-inflammatory properties of sage and its components have been assessed in several *in vitro* experiments. Li et al. (2019) studied the anti-inflammatory effect of 12 diterpenoid compounds fractionated from sage (eight were newly identified molecules) in murine macrophages. Among the 12 diterpenoids, compound 7 was the most potent to inhibit NO production with an IC_{50} value of 3.10 μg/mL.

Compound 7 was selected for molecular docking studies and inflammatory therapeutic targets such as iNOS, COX-2, c-Jun N-terminal kinase, P38, TNF-α, sirtuin 2, IL-5, and Janus family of protein tyrosine kinases gene were explored; compound 7 exerted inhibitory effects on over-expression of LPS-induced iNOS and COX-2 *via* suppressing the phosphorylation of c-Jun N-terminal kinase in the MAPK signaling pathway, a central therapeutic target in the control of inflammation. Sage was among the herbs examined by Mueller et al. (2010) for anti-inflammatory activity in the standard LPS-stimulated RAW264.7 murine macrophage model. The results showed that sage extract improved the anti-inflammatory profile of the secreted cytokines by decreasing IL-6 and TNF-α, but also IL-10, the anti-inflammatory cytokine, while the expression of iNOS was inhibited. Using the same cellular model, Brindisi et al. (2021) investigated the extracts of sage leaves and flowers harvested in Southern Italy and found a decrease in NO production mediated *via* NF-κB inhibition and a decline in the expression of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α associated to reduction of intracellular reactive oxygen species (ROS). In further *in vitro* studies, Russo et al. (2021) investigated the effects of sage alcoholic extracts in IL-β-stimulated neuroblastoma cells and human subcutaneous mature adipocytes. Both cell models were treated with two doses of sage extract in the presence or absence of IL-β and incubated for 4 or 24 h. MCP-1, IL-6, IL-8, and TNF-α basal levels were decreased in adipocytes after acute treatment with sage, whereas in neuroblastoma cells sage increased the basal levels of many cytokines and chemokines at both protein and transcriptional level. In an *in vivo* experiment, Ben Khedher et al. (2018) found that oral treatment of mice with diet-induced obesity with a low-dose methanolic sage extract for 5 weeks increased plasma levels of anti-inflammatory cytokines IL-2, IL-4, and IL-10 and reduced levels of pro-inflammatory cytokines IL-12, TNF-α, and keratinocyte-derived chemoattractant/human growth-regulated oncogene. Thus, sage also appears to be a relevant immunomodulatory herbal product.

3.11. Thyme

Thyme is an aromatic perennial plant originating in the Mediterranean region that is widely used in food spicing and preservation and for various purposes in folk medicine. Its immunomodulatory properties have been examined in several experimental studies. Vigo, Cepeda, Gualillo, and Perez-Fernandez (2004) showed an anti-inflammatory effect of thyme extracts in LPS- and IFN-γ-stimulated murine macrophages by demonstrating inhibition of iNOS miRNA expression. Among the herbs studied by Mueller et al. (2010) for anti-inflammatory effects in the LPS-stimulated RAW 264.7 murine macrophage model, addition of thyme extract to the cell culture resulted in reduced secretion of pro-inflammatory IL-6 and TNF-α, but also of anti-inflammatory IL-10, while iNOS expression was strongly inhibited. The immunomodulatory effects of thyme and its constituent thymol were also studied by Amirghofran, Hashemzadeh, Javidnia, Golmoghaddam, and Esmaeilbeig (2011) in cell proliferation assays of human blood lymphocytes and a Jurkat cell line. Results showed a dose-dependent inhibitory effect of thyme extracts on mitogen-induced lymphocyte proliferation at concentrations $>$ 50 μg/mL, with an IC_{50} = 53.3 μg/mL. Thymol also inhibited growth of Jurkat cells, which are considered to be similar to resting T-lymphocytes, thus showing its capability to inhibit cell growth of peripheral blood mononuclear cells. The *in vitro* anti-inflammatory effect of thyme was also demonstrated by De Oliveira et al. (2017), who showed a dose-dependent reduction in the production of pro-inflammatory cytokines IL-1β and TNF-α in the conventional LPS-stimulated murine macrophage cell culture model. Besides peppermint, Osman et al. (2020) examined the immune effects of an oral thyme extract in the murine model of systemic inflammation induced by oxidized palm oil feeding. Results showed that thyme extract increased serum immunoglobulin G, immunoglobulin M, and immunoglobulin A and reduced CRP, IL-1, IL-6, TNF-α, and MCP-1 levels, thus reverting in part the inflammatory abnormalities of the model. Thus, experimental evidence is mounting on the immunomodulatory properties of thyme.

3.12. Concluding remarks

To sum up, the main medicinal herbs and their key bioactive compounds with promising immunomodulatory properties that are discussed in this review include: bay laurel (1,8-cineole) (Lee et al., 2019), black cumin (TQ and α-hederin) (Hossen et al., 2017), clove (eugenol and isoeugenol) (Bachiega et al., 2012), fennel (anethole) (Darzi et al., 2018), lemon balm (caffeic acid and chlorogenic acid) (Drozd & Anuszewska, 2003), lemongrass (citral and linalool) (Bachiega & Sforcin, 2011), marjoram (rosmarinic acid) (Arranz et al., 2019), peppermint (menthol and menthone) (Zaia et al., 2016), rosemary (carnosic acid and carnosol) (Arranz et al., 2015a), sage (rosmarinic acid, carnosic acid, carnosol, ursolic acid, and luteolin-7-*O*-glucoside) (Brindisi et al., 2021), and thyme (thymol) (Amirghofran et al., 2011). These herbal extracts and their bioactive constituents possess immunomodulatory and anti-inflammatory effects, albeit to a different extent. Black cumin, clove, lemongrass, rosemary, sage, and thyme have been extensively studied in *in vitro* (cell) and *in vivo* (animal) models, but clinical studies are lacking. It is, therefore, of great importance to conduct dedicated randomized clinical trials in subjects of diverse demographics to confirm the promising experimental data favoring immunomodulation.

4. Immunomodulatory effects (epidemiological, *in vitro*, and *in vivo* studies) of selected herb essential oils

The evidence from experimental and clinical studies on the immunomodulatory effects of medicinal herb-derived essential oils is detailed in Table 2.

4.1. Bay laurel

Bay laurel essential oil has a wide range of usage in traditional medicine. Pérez-Rosés et al. (2015) examined the immunomodulatory activity of bay laurel oil by testing its inhibitory capacity of human neutrophil phagocytosis assessed by flow cytometry and the inhibition of the alternative and classical pathways of complement activation in a hemolytic assay. Results showed a nearly 40% inhibition of phagocytosis at 46 μg/mL, inhibition of the classical pathway of complement activation at a moderate IC_{50} value of 75 μg/mL, and no effect on the alternate pathway of complement.

4.2. Black cumin

Black cumin essential oil has recently been investigated in experimental studies for its anti-inflammatory and immunomodulatory effects. Silva, Haris, Serralheiro, and Pacheco (2020) carried out various *in vitro* studies in human mammary carcinoma (MCF-7) and melanoma (A375) cell lines treated with 1 mL of 0.002% w/v 2,2-diphenyl-1-picrylhydrazyl solution in dimethyl sulfoxide. Clove essential oil volatiles increased the stabilization of protein structures, whereas non-volatile compounds (mainly TQ) increased antioxidant activity, POTE ankyrin domain family member F and Heat Shock Protein 90-β expression, enzyme inhibition, and cytotoxic activity in cancer cells. Clove essential oil also increased antitumor activity and the ability to target acetylcholinesterase and 3-hydroxy-3-methylglutaryl coenzyme A reductase. Ozugurlu et al. (2005) reported that black cumin essential oil protected the central nervous tissue against rat autoimmune encephalomyelitis. It also decreased the production of ROS and NO levels in the brain while increasing NO levels in the medulla spinalis. The molecular docking studies of Bouchentouf and Missoum (2020) showed that both black cumin seeds and their essential oil inhibited COVID-19 and SARS virus.

Table 2
The immunomodulatory effects of selected herb essential oils determined by *in vitro* and *in vivo* studies.

Herb oils	Study design	Cell or animal type	Extraction method	Treatment	Outcomes*	Author (year)
Bay laurel	*in vitro* (cell culture)	Human neutrophils (flow cytometry) and complement activation (hemolytic assay)	Commercial product	Different oil dilutions in Hanks' balanced salt solution with 10% DMSO	↑ Inhibition of phagocytosis at 46 μg/mL ↑ Inhibition of classical complement pathway activation (IC_{50} 75 μg/mL) ↔ Inhibition of alternate complement pathway activation	Pérez-Rosés et al. (2015)
Black cumin	*in vitro* (cell culture)	MCF-7 and A375 human cancer cell lines	Commercial product	10 μL of oil or different concentrations of non-volatile sample added to DPPH solution in DMSO	↑ Stabilization of protein structures by volatiles ↑ Antitumor activity and ability to target AChE and HMGR ↑ Antioxidant activity by non-volatile compounds, (mainly TQ) ↑ Expression of POTEF and HSP 90-β ↑ Enzyme inhibition ↑ Cytotoxic activity in cancer cells	Silva et al. (2020)
		Rats with experimental autoimmune encephalomyelitis	na	Oil given by oral gavage	↑ Protection of central nervous system tissues ↓ ROS production ↓ Brain NO level ↑ Medulla spinalis NO level ↓ Oxidative stress ↑ Antioxidant and regulatory effects *via* inflammatory cells	Ozugurlu et al. (2005)
	Molecular docking	na	Commercial product &maceration (hexane)	na	↑ Inhibition of COVID-19 and SARS viruses by acting on the main protease M^{pro} ↑ 6LU7 active site docking with energy score − 6.29734373 kCal/mol by nigelledine ↑ 2GTB active site docking with energy score − 6.50204802 kCal/mol by α-hederin Better or equal results to FDA approved drugs	Bouchentouf and Missoum (2020)
Clove	*in vitro* (cell culture)	Peritoneal macrophages from male BALB/c mice, activated by LPS (5 μg/mL)	Hydro distillation	Cloveessential oil (5–100 μg per well)	↓ IL-1β and IL-6 production dose-dependently	Rodrigues et al. (2009)
		Human neutrophils (flow cytometry) and complement activation (hemolytic assay)	Commercial product	Different dilutions of oil and eugenol in Hanks' balanced salt solution with 10% DMSO	↑ Inhibition of phagocytosis at 50 μg/mL clove oil and 58 μg/mL eugenol ↑ Inhibition of classical complement pathway activation (IC_{50} 75 μg/mL clove oil and 78 μg/mL eugenol) ↔ Inhibition of alternate complement pathway activation	Pérez-Rosés et al. (2015)
		Human dermal fibroblast cell line (HDF3CGF) stimulated with a mixture of IL-1β, TNF-α, IFN-γ, bFGF, EGF, and PDGF	Commercial product	Clove oil at 0.011, 0.0037, 0.0012, and 0.00041%, v/v	↓ VCAM-1, IP-10, I-TAC, and MIG levels ↓ M-CSF and PAI-1 levels ↑ Anti-proliferative and anti-inflammatory activity	Han et al. (2017)
		Murine macrophages RAW 264.7 stimulated with LPS, 0.1 μg/mL	Steam distillation	Clove oil concentrations ranging from 0.98 to 1000 μg/mL	At 100 μg/mL: ↑ iNOS production ↓ IL-6 secretion	Lang et al. (2019)
		U937 cells and bovine arterial endothelial cells	Commercial product	0.01% concentration	↓ LPS-induced COX-2 promoter activity 40% ↑ PPAR-α agonistic activity	Hotta et al. (2010)
	in vivo (animal)	Male Swiss mice with cyclophosphamide-immunosuppression, immunized with sheep red blood cells	Commercial product	100, 200, and 400 mg/kg of essential oil, orally (by gavage)	↑ Total WBC count ↑ Cell-mediated immunity and humoral immunity ↑ Protection against immunosuppression caused by cyclophosphamide ↑ DTH response	Carrasco et al. (2009)
Fennel	*in vitro* (cell culture)	Human PMN cells from healthy volunteers THP-1 (human monocytic	Hydro distillation	25 g/mL	↓ ROS produced from whole blood phagocytes ↓ TNF-α production	Orhan et al. (2016)

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Table 2 (*continued*)

Herb oils	Study design	Cell or animal type	Extraction method	Treatment	Outcomes*	Author (year)
		leukemia) cells stimulated with LPS				
		Porcine alveolar macrophages collected by bronchoalveolar lavage, stimulated with LPS (1 μg/mL)	Essential oil synthetically produced but identical to the natural compounds and > 95% pure	0, 25, 50, 100, and 200 μg/mL	↓ IL-1β and TNF-α levels ↓ TGF-β levels	Liu et al. (2012)
	in vivo (animal)	Male Wistar rats with acetic acid-induced colitis	Hydro distillation	Fennel oil, 100, 200, and 400 mg/kg by oral gavage for 5 days post-induction of colitis	At 200 and 400 mg/kg doses: ↓ Macro and microscopic colonic inflammation In colon homogenate: ↓ MPO activity ↓ Expression of TNF-α positive cells ↓ Expression of NF-κB	Rezayat et al. (2018)
Lemon balm	*in vivo* (animal)	Male Wistar rats with carrageenan-induced paw edema	Hydro distillation	200 and 400 mg/kg, orally	↓ Edema 6 h after administration	Bounihi et al. (2013)
Lemongrass	*in vitro* (cell culture)	Peritoneal macrophages from BALB/C mice, stimulated with DMSO (0.2%) or LPS (5 μg/mL)	Hydrodistillation	5, 10, 25, 50, and 100 μg per well	↓ IL-1β and IL-6 production	Sforcin et al. (2009)
		Peritoneal macrophages from BALB/c mice, stimulated with LPS (5 μg/mL)	Commercial product	Citral at 25, 50, and 100 μg/well for IL-1β and 5, 10, 25, 50, and 100 μg/well for IL-6 and IL-10	↓ IL-1β and IL-6 production ↓ IL-10 production	Bachiega and Sforcin (2011)
	in vivo (animal)	Wistar rats with formol-induced edema	Steam distillation	2,000 and 3,000 mg/kg, orally	↓ Dose-dependent edema over time	Gbenou et al. (2013)
		Swiss albino mice with carrageenan-induced paw edema and croton oil-induced ear edema	Steam distillation	10, 40, 100, or 200 mg/kg, orally Topical application at doses of 5 and 10 mL/ear	↓ Skin inflammatory response ↓ Paw edema	Boukhatem et al. (2014)
Marjoram	*in vitro* (cell culture)	THP-1 human macrophages stimulated with LPS or ox-LDL	SFE	5 and 7.5 μg/mL	↓ IL-1β and IL-6 production in LPS-stimulated macrophages ↓ TNF-α, IL-1β, IL-6, and IL-10 production in ox-LDL stimulated cells	Arranz et al. (2015b)
		Human neutrophils (flow cytometry) and complement activation (hemolytic assay)	Commercial product	Carvacrol at different dilutions in Hanks' balanced salt solution with 10% DMSO	↑ Inhibition of phagocytosis < 25% at highest dose tested ↑ Inhibition of classical complement pathway activation (IC_{50} 78 μg/mL) ↔ Inhibition of alternate complement pathway activation	Pérez-Rosés et al. (2015)
Peppermint	*in vitro* (cell culture)	Murine macrophages RAW 264.7 stimulated with LPS, 0.1 μg/mL	Commercial product	Concentrations of mint oil ranging from 0.98 to 1000 μg/mL	At 100 μg/mL: ↓ Phagocytosis by 42% ↓ IL-6 secretion ↔ iNOS production	Lang et al. (2019)
Rosemary	*in vitro* (cell culture)	Human leukocytes with positive control of LPS	Commercial product	Inhibition of phagocytosis: 48.40 μg/mL	↑ Inhibition of phagocytosis	Pérez-Rosés et al. (2015)
	in vivo (animal)	ICR mice with carrageenan-induced paw edema and colitis induced by TNBS	Commercial product	Various doses of rosemary oil in the standard laboratory diet starting 2 weeks before the experiments	↓ paw edema ↓ paw MPO activity ↓ Colonic inflammation (high dose) ↓ MPO activity and IL-6 levels in colon tissue (low dose)	Juhás et al. (2009)
		Wistar male rats and Swiss male albino mice with ear edema induced by croton oil	Hydro distillation	300 mg/kg essential oil solubilized in Tween 80 and then suspended in water, orally for 6 days	↓ Granulomatous tissue formation by 59% ↓ Ear edema by 77%	Faria et al. (2011)
		Male Wistar rats and Swiss mice with carrageenan-induced paw edema	Commercial product	Rosemary oil and its nanoemulsion administered orally 30 min prior to starting the experiments	↓ paw edema by oil at 100 mg/kg and by oil nanoemulsion at 498 μg/kg ↓ Gastric H_2S production in all of the measurement phases by the same doses of oil and oil nanoemulsion	Borges et al. (2018)
Sage	*in vitro* (cell culture)	Murine macrophages RAW 264.7 stimulated with LPS, 1 μg/mL	Hydro distillation Hydro distillation	Sage oil at concentrations of 0.16, 0.32, 0.64, and 1.25 μL/mL	↓ NO production dose-dependently	Abu-Darwish et al. (2013)

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Table 2 (*continued*)

Herb oils	Study design	Cell or animal type	Extraction method	Treatment	Outcomes*	Author (year)
	in vivo (animal)	Male BALB/c mice with circular full-thickness surgical wounds		2 and 4 % (w/w) essential oil topically on wound daily for 14 days	Accelerated wound healing: ↓ Expression of IL-1β, IL-6, and TNF-α ↑ Expression of FGF-2 and VEGF-1	Farahpour et al. (2020)
Thyme	*in vitro* (cell culture)	Human monocytic leukemia THP-1 cells stimulated with 1 μg/mL of LPS	Maceration (petroleum ether and methanol)	0.01 μL/mL of thyme essential oil dispersed by 1 mL 25% ethanol	↓ IL-1β, IL-8, and TNF-α secretion	Tsai et al. (2011)
		BALB/c mice mammary epithelial cells stimulated with 1 μg/mL of LPS	na	10, 20, and 40 μg/mL of thymol	↓ IL-6 and TNF-α levels ↓ iNOS and COX-2 expression ↓ Phosphorylation of IκBα, NF-κB, ERK, JNK, and p38 MAPKs	Liang et al. (2014)
		Bovine serum albumin	Commercial product	0.5 μL/mL	↓ Protein denaturation (IC_{50} = 6.8 μL/mL)	Boukhatem et al. (2020)
	in vivo (animal)	Male Wistar rats with carrageenan-induced pleurisy and male Swiss mice with croton oil-induced ear edema	Steam distillation	Oral pre-treatment with thyme oil, thymol, and carvacrol at different doses	↓ Exudate and leukocytosis in the pleurisy model by thyme oil, thymol, and carvacrol ↓ Ear edema only by carvacrol	Fachini-Queiroz et al. (2012)
		Randomized trial in male broiler chicks	Commercial product	Thymol + carvacrol at 0, 60, 100, and 200 mg/kg of feed for 42 days	↑ Hypersensitivity response, total, and IgG anti-sheep red blood cell titters ↓ Heterophils/lymphocytes ratio ↑ Antioxidant activity in muscle	Hashemipour et al. (2013)
		New Zealand rabbits (infected with *Coccidia* and treated with TEO)	Commercial product	Gastric gavage at a dose of 500 mg/kg bw	↓ Oocyst shedding	Abu El Ezz et al. (2020)
	in vivo (randomized clinical trial)	83 patients with confirmed COVID-19 infection (n = 43) control (n = 40) thyme essential oil intervention	Commercial product	5 mL of the syrup or essential oil 3 times per day for one week, orally	↓ Symptoms of coronavirus infection ↓ Neutrophil count ↑ Lymphocyte count	Sardari et al. (2021)

Abbreviations: AChE, acetylcholinesterase; bFGF, basic fibroblast growth factor; bw, body weight; COX-2, cyclooxygenase-2; COVID-19, coronavirus disease of 2019; DMSO, dimethyl sulfoxide; DPPH, 2,2-diphenyl-1-picrylhydrazyl; DTH, delayed-type hypersensitivity; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; FDA, Food and Drug Administration; FGF, fibroblast growth factor; GTB, glycosyltransferases B; HMGR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HSP, heat-shock protein; IC_{50}, the half-maximal inhibitory concentration; IFN-γ, interferon-gama; IgG, Immunoglobulin G; I-TAC, interferon-inducible T-cell a chemoattractant; IL, interleukin; IP-10, interferon gamma-induced protein 10; IκBα, inhibitor protein of NF-κB; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; M-CSF, macrophage-colony stimulating factor; MIG, monokine induced by interferon gamma; MAPKs, mitogen-activated protein kinases; MPO, myeloperoxidase; na, not available; NF-κB, nuclear factor-kappa B; NO, nitric oxide; ox-LDL, oxidized low-density lipoprotein; PAI, plasminogen activator inhibitor; PDGF, platelet-derived growth factor; PMN, polymorphonuclear neutrophils; POTEF, POTE ankyrin domain family member F; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SARS, severe acute respiratory syndrome; SFE, supercritical fluid extraction; TEO, *Thymus vulgaris* essential oil; TGF, transforming growth factor; THP-1, Tohoku Hospital Pediatrics-1; TNBS, trinitrobenzene sulfonic acid; TNF-α, tumor necrosis factor-alpha; TQ, thymoquinone; VEGF, vascular endothelial growth factor; VCAM-1, vascular cell adhesion molecule-1; WBC, white blood cell.

* Results: ↑, ↓, and ↔ present significant increase, significant decrease, and non-significant effect, respectively.

4.3. Clove

Several studies have investigated the essential oil of clove for its immune-enhancing properties. Besides examining the anti-inflammatory effects of aqueous clove extract in a murine model, Rodrigues et al. (2009) conducted an *in vitro* study with mouse peritoneal macrophages exposed to various concentrations of clove essential oil, which main component was eugenol. Results showed a strong dose-dependent inhibition of IL-1β and IL-6 production. Pérez-Rosés et al. (2015) investigated the *in vitro* activity of clove essential oil and pure compound eugenol on human neutrophils and the complement system. Clove essential oil inhibited phagocytosis at a concentration of 50.4 μg/mL, with a profile very similar to that of eugenol (57.6 μg/mL). Eugenol and clove oil also had similar IC_{50} values in the inhibition of the classical complement pathway activation. Clove terpenes showed almost no activity, indicating that eugenol is the main active constituent of clove oil. In an *in vitro* assay of stimulated human dermal fibroblasts investigated by Han, Parker, and Dorsett (2017), clove essential oil modulated important signaling pathways related to immune function, cell cycle control, cellular stress responses, and cancer biology. They observed anti-proliferative activity and decreased levels of inflammatory biomarkers such as vascular cell adhesion molecule-1, interferon gamma-induced protein 10, interferon-inducible T-cell a chemoattractant, and monokine induced by interferon gamma. Moreover, the effect of 0.011% clove essential oil on genome-wide gene expression showed anti-inflammatory, immunomodulatory, and tissue remodeling effects in the human skin disease model. In another study, Lang et al. (2019) examined clove essential oil containing 80.5% eugenol for its immunomodulatory effects in a murine macrophage cell line. The results showed that pretreatment with 100 μg/mL clove induced production of iNOS and reduced the secretion of IL-6. Hotta, Nakata, Katsukawa, Hori, Takahashi, and Inoue (2010) further showed in a bovine endothelial cell model that clove essential oil at 0.01% suppressed LPS-induced COX-2-promoter activity by 40% and activated peroxisome proliferator-activated receptor-α. Furthermore in an *in vivo* study in a mouse model of immunosuppression, Carrasco et al. (2009) observed that clove essential oil containing 98% eugenol stimulated cell-mediated immunity and restored white blood cell count and humoral immunity.

4.4. Fennel

Fennel essential oil is known for its anti-proliferative, antitumor, and anti-metastatic properties (Syed, Elkady, Mohammed, Mirza, Hakeem, & Alkarim, 2018). Orhan, Mesaik, Jabeen, and Kan (2016) studied the effects of essential oils and phenolic derivatives of various herbs, one of which was fennel, on human cellular immune responses. Fennel

essential oil was one of the oils that showed stronger inhibition of oxidative burst from whole blood phagocytes. *Trans*-anethole, the main component of fennel essential oil, dose-dependently decreased IL-1β and TNF-α levels; however, it also reduced the levels of TGF-β, a cytokine that can act both as pro- and anti-inflammatory (Liu, Song, Che, Bravo, & Pettigrew, 2012). Rezayat et al. (2018) used an *in vivo* murine model of experimental colitis to assess the anti-inflammatory effects of fennel essential oil. Oral administration at 200 and 400 mg/kg after induction of colitis with intra-rectal acetic acid mitigated colonic inflammation and significantly reduced the levels of myeloperoxidase in colonic tissue, as well as the expression of TNF-α and NF-κB. These data support the anti-inflammatory properties of fennel essential oil.

4.5. Lemon balm

Lemon balm has been used in traditional medicine for a variety of purposes, among them as antispasmodic and for heart-strengthening effects. Bounihi, Hajjaj, Alnamer, Cherrah, and Zellou (2013) investigated the anti-inflammatory effects of lemon balm essential oil consisting of nerol (30.44%), citral (27.03%), isopulegol (22.02%), caryophyllene (2.29%), caryophyllene oxide (1.24%), and citronella (1.06%) in Wistar rats with carrageenan-induced paw edema. Results showed a significant reduction of edema at the doses of 200 and 400 mg/kg, illustrating a strong anti-inflammatory effect of lemon balm essential oil.

4.6. Lemongrass

Lemongrass essential oil, with citral as the main constituent, has been widely used as traditional medicine as an antimicrobial, antioxidant, antifungal, and anti-inflammatory agent. In LPS-stimulated mouse peritoneal macrophages, application of lemongrass essential oil (primary components, citral and linalool) and citral alone resulted in an inhibition of IL-1β and IL-6 secretion, respectively (Sforcin et al., 2009) and reduction in IL-1β secretion and IL-10 production (Bachiega & Sforcin, 2011). Gbenou et al. (2013) investigated the anti-inflammatory effect of lemongrass essential oil on a rat model of edema and showed a significant dose-dependent prevention of edema over time. Boukhatem, Ferhat, Kameli, Saidi, and Kebir (2014) also examined the topical and oral effects of lemongrass essential oil in mouse models of paw and ear edema and showed both oral and topical dose-dependent anti-inflammatory effects.

4.7. Marjoram

Marjoram essential oil contains several bioactive constituents such as terpinene-4-ol, sabinene hydrate, thymol, and carvacrol. These compounds have been reported to exert several health benefits, including immunomodulatory effects. To evaluate the possible mechanism, Arranz, Jaime, López de las Hazas, Reglero, and Santoyo (2015b) investigated the anti-inflammatory activities of marjoram essential oil (mainly sabinene hydrate and terpineol) in activated THP-1 human macrophages. The results showed significantly reductions of IL-1β and IL-6 production in LPS-stimulated cells and significant decreases in IL-1β, IL-6, IL-10, and TNF-α production in oxidized low-density lipoprotein (ox-LDL) stimulated cells. In that study, it was also reported that supercritical extract of marjoram essential oil decreased COX-2 and NF-κB gene expression. Among other herb oils and their components, Pérez-Rosés et al. (2015) examined the immunomodulatory activity of carvacrol, the major fraction of marjoram oil, in a cell culture model of human neutrophils. Results showed a weak inhibition of phagocytosis, inhibition of the classical pathway of complement activation at a moderate IC_{50} value of 78 μg/mL, and no effect on the alternate pathway of complement.

4.8. Peppermint

Current studies have explored the medicinal potential as anti-inflammatory agent of peppermint essential oil. In the same LPS-activated murine macrophage cell line used to investigate the immunomodulatory effects of clove essential oil, Lang et al. (2019) assessed a peppermint essential oil composed mainly of menthol (32.5%) and (DL)-menthone (26.3%). The results showed that pretreatment with 100 μg/mL clove induced a 42% inhibition of phagocytosis and reduced secretion of IL-6, but had no effect on iNOS production.

4.9. Rosemary

The main components of rosemary essential oil are α-pinene, 1,8-cineole, camphor, myrcene, and camphene, and they may vary depending on the weather, soil, and extraction methods, among others. Rosemary essential oil has been reported for its antioxidant, antimicrobial, neuroprotective, and anti-inflammatory properties (Arranz et al., 2015a). In studies similar to those of various herbal oils using a human neutrophil culture model, Pérez-Rosés et al. (2015) examined the immunomodulatory activity of rosemary essential oil. Results showed a significant inhibition of phagocytosis, although it was $< 25\%$ at the highest tested concentration. For the inhibition of the classical pathway of complement system, rosemary essential oil showed 27% inhibition at an IC_{50} of 155 μg/mL.

Other studies have involved animal models. Juhás, Bukovská, Čikoš, Czikková, Fabian, and Koppel (2009) examined the effect of rosemary essential oil in mice with carrageenan-induced paw edema and solvent-induced colitis. Results indicated that 5,000 ppm of rosemary essential oil added to the chow for 2 weeks before the experiments increased the extent of paw edema after 2 h, but suppressed it after 24 h, together with reduction of myeloperoxidase activity in paw tissue. In the colitis model, macroscopic scores for colonic inflammation were significantly decreased at a dose of 2,500 ppm, while myeloperoxidase activity and IL-6 levels in colon tissue were significantly decreased at the dose of 1,250 ppm. The effects of rosemary essential oil in inflammatory and nociceptive murine models with Croton oil-induced ear edema were also studied by Faria, Lima, Perazzo, and Carvalho (2011). Results showed that oral doses of 300 mg/kg of the oil for 6 days inhibited granulomatous tissue formation by 59% and ear edema by 77%. In addition, Borges et al. (2018) evaluated the anti-inflammatory and analgesic potency of essential oil of rosemary and its nanoemulsion administered orally 30 min before starting the experiments in murine models of paw edema. Both forms inhibited the maximum peak of rat paw edema, the standard oil at a dose of 100 mg/kg and the oil nanoemulsion at 498 μg/kg. In an assay for gastric H_2S production, the same doses of oil and oil nanoemulsion inhibited H_2S production in all of the measurement phases. The findings suggested that the oil nanoemulsion form was efficacious as anti-inflammatory agent at doses 600-fold lower than those of the essential oil of rosemary itself.

4.10. Sage

Sage essential oil, composed of monoterpenes, sesquiterpenes, and phenolics (Vosoughi, Gomarian, Pirbalouti, Khaghani, & Malekpoor, 2018), is a widely used herbal medicine for ailments of the nervous system, heart and blood circulation, respiratory and digestive systems, as well as metabolic and endocrine diseases. Abu-Darwish et al. (2013) examined the anti-inflammatory effects of sage oil obtained from the aerial parts of the plant in a cell culture model of LPS-stimulated murine macrophages. Results disclosed a dose-dependent inhibition of NO production. Farahpour, Pirkhezr, Ashrafian, and Sonbolid (2020) studied the effects of topical application of sage essential oil in a murine model of infected wound. Results showed that sage essential oil shortened the inflammatory phase by reducing the expression of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, and accelerating

cellular proliferation, collagen deposition, re-vascularization, and re-epithelization *via* increased expression of growth factors.

4.11. Thyme

Thyme essential oil is one of the most aromatic and medicinal plant oils used worldwide. The oil, consisting of two main components, thymol and carvacrol, has antioxidant, antimicrobial, antitussive, antibacterial, and anti-inflammatory effects (Fachini-Queiroz et al., 2012). Tsai, Lin, Lin, and Yang (2011) studied *in vitro* the anti-inflammatory activity of thyme essential oil in stimulated THP-1 cells and found a strong antioxidant activity and reduced secretion of pro-inflammatory cytokines IL-1β, IL-8, and TNF-α. An additional study examined the anti-inflammatory effects of thymol, the main component of thyme essential oil, in LPS-stimulated mouse mammary epithelial cells (Liang et al., 2014). The results showed a dose-dependent reduction of the production of IL-6 and TNF-α and inhibition of iNOS and COX-2 expression, and this anti-inflammatory activity occurred *via* interfering the activation of NF-κB and MAPK signaling pathways. Boukhatem et al. (2020) determined both *in vitro* and *in vivo* anti-inflammatory activities of thyme essential oil by a protein denaturation assay and inhibition of croton oil-induced ear edema in mice, respectively. The results showed a potent anti-inflammatory effect of thyme essential oil and its component carvracol.

Other *in vivo* studies examined the immunomodulating effects of thyme essential oil. Fachini-Queiroz et al. (2012) used rodent models of experimental pleurisy and ear edema and reported that thyme oil, thymol and carvacrol inhibited inflammatory edema in the pleurisy model, while only thymol reduced edema in the ear edema model. In another study, Hashemipour, Kermanshahi, Golian, and Veldkamp (2013) fed broiler chickens thymol and carvacrol supplements in feed and observed a dose-related improvement in immune responses and increased antioxidant activity in muscle. An additional study by Abu El Ezz, Aboelsoued, Hassan, Abdel Megeed, and El-Metenawy (2020) showed the therapeutic effect of thyme essential oil on hepatic coccidiosis in infected rabbits. The effect of thyme essential oil on symptoms of COVID-19 patients was recently investigated in a randomized controlled trial by Sardari, Mobaien, Ghassemifard, Kamali, and Khavasi (2021). The results showed that 5 mL of syrup or thyme essential oil 3 times per day for one week mitigated the symptoms of SARS-CoV-2 while decreasing neutrophil and increasing lymphocyte counts.

4.12. Concluding remarks

To summarize, the main herbal essential oils and their bioactive compounds with promising immunomodulatory properties in experimental studies that are discussed in this review include: bay laurel (1,8-cineole) (Pérez-Rosés et al., 2015), black cumin (TQ) (Silva et al., 2020), clove (eugenol and terpenes) (Rodrigues et al., 2009), fennel (trans-anethole) (Liu et al., 2012), lemon balm (nerol, citral, and isopulegol) (Bounihi et al., 2013), lemongrass (citral and linalool) (Sforcin et al., 2009), marjoram (terpinene-4-ol, sabinene hydrate, thymol, and carvacrol) (Arranz et al., 2015b), peppermint (menthol and (DL)-menthone) (Lang et al., 2019), rosemary (α-pinene, and 1,8-cineole) (Borges et al., 2018), sage (1,8-cineole and camphor) (Abu-Darwish et al., 2013), and thyme (thymol and carvacrol) (Fachini-Queiroz et al., 2012). Within these essential oils, those extracted from black cumin, clove, rosemary, and thyme have been studied extensively in different *in vitro* and *in vivo* models. Only thyme has been studied for immune effects in covid-19 patients, with promising effects. The eleven herbal extracts selected show immunomodulatory properties, albeit with different scopes.

5. Safety and toxicity of selected herb extracts and their essential oils

The main experimental studies evaluating the safety and toxicity of selected herb extracts and their essential oils are summarized below.

5.1. Bay laurel

The safety and toxicology of bay laurel have been investigated *via* cytotoxicity studies. El-Sawi, Ibrahim, and Ali (2009) disclosed growth inhibition effects by bay laurel essential oil in human liver, breast, lung, and brain cancer cell lines with IC_{50} values of 0.6, 0.8, 0.9, and 1.8 μg/mL, respectively. The toxicity of bay laurel was also investigated in an acute lung injury mouse model and no cytotoxic effects were observed at different doses (25, 50, 100, and 200 μg/mL) (Lee et al., 2019). Additional toxicology studies by Kazeem, Omotayo, Ashafa, and Olugbemiro (2015) confirmed the weak toxicity of bay laurel, which exhibited high lethal dose values in both a cytotoxicity brine shrimp survival assay [lethal dose 50 (LD_{50}) of 1,100 μg/mL] and a duckweed (*Lemna minor*) phytotoxicity assay (LD_{50} of 700 μg/mL).

5.2. Black cumin

Although considered safe for short-term use in food and for medicinal purposes, scant information is available on black cumin's safety in high amounts for various health conditions. Standard doses of oral black cumin essential oils taken for 56 days by male Sprague Dawley rats were safe concerning biochemical and hematologic variables and the histological examination of major organs (Sultan, Butt, & Anjum, 2009). In a *meta*-analysis of 11 randomized controlled trials of black cumin assessing its anti-hypertensive effect, 500 mg to 2 g/day of powder or up to 3 g/day of oil administered for 4 to 12 weeks was found to have a blood pressure lowering effect and to be generally well tolerated, with no studies reporting serious adverse events (Sahebkar et al., 2016). However, black cumin may influence the metabolism of a wide range of drugs; therefore, medical advice is required before using it for therapeutic purposes (Kulyar, Li, Mehmood, Waqas, Li, & Li, 2020). According to Silva et al. (2020), black cumin, defined as Generally Recognized as Safe by the FDA, is marketed as both food and natural medicine, although it appears to have higher cytotoxicity due to its volatile monoterpenes when compared with oils and extracts from other seeds.

5.3. Clove

There have been numerous studies investigating the toxicity and safety of clove extract and its essential oil. In an *in vitro* assay using murine peritoneal macrophages conducted by Bachiega et al. (2012), clove and eugenol did not affect cell viability at concentrations ranging from 5 to 100 mg/well during 24-hour assays. Dibazar et al. (2015) showed that clove extracts did not affect cell survival in cultures of mouse macrophages except at high concentrations (>100 mg/mL), when cytotoxicity was mainly due to eugenol. Clove oil is used as topical application to relieve pain and promote healing; thus, it was a reason for concern when in an *in vitro* study, a concentration of 0.03% clove oil was highly toxic to human fibroblasts and endothelial cells, most cytotoxic activity being due to eugenol (Prashar, Locke, & Evans, 2006). In addition, in a case report by Janes, Price, and Thomas (2005), accidental ingestion of 10 mL of clove oil by a 15-month-old boy resulted in fulminant hepatic failure. According to Batiha, Alkazmi, Wasef, Beshbishy, Nadwa, and Rashwan (2020), clove has detoxification and cardiac health effects in humans by reducing lipid peroxidation and increasing levels of the endogenous redox enzyme. Nevertheless, the FDA has confirmed the safety of clove buds, clove oil, eugenol, and oleoresins as food supplements with an acceptable daily amount of 2.5 mg/kg body weight.

5.4. Fennel

Ostad, Soodi, Shariffzadeh, Khorshidi, and Marzban (2001)

conducted acute toxicology studies of fennel essential oil in female Sprague-Dawley rats by giving different oral doses *via* gavage and observed universal lethality at the 1,500 mg/kg dose. Using lower doses, the LD_{50} value was estimated at 1,326 mg/kg. In groups of rats given 1,000 to 1,250 mg/kg non-lethal doses, the main adverse effect was sedation and no obvious damage was observed in vital organs. Estragole, an alkenylbenzene shown to be genotoxic and hepatotoxic in rodents, is a common component of herbs and spices, being particularly abundant in fennel (Gori, Gallo, Mascherini, Mugelli, Vannacci, & Firenzuoli, 2012). The estragole-containing preparations of fennel seed and fennel seed essential oil were analyzed for their ability to cause cytotoxicity and genotoxicity in a human hepatoma cell line (Levorato et al., 2018). None of the tested concentrations of fennel seed powder induced deoxyribonucleic acid damage, nor apoptosis or cell cycle perturbation. Fennel seed extract and essential oil did not affect cell viability in 4-hour assays at doses from 0.3 to 40 μg/mL and 0.015 to 2 μg/mL, respectively, but the higher doses of each fennel preparation were cytotoxic in 24-hour assays. The data support the hypothesis that genotoxicity is substantially reduced when estragole is given as part of complex herbal mixtures, in which other bioactives (*i.e.*, polyphenols) may counteract its toxic effects (Gori et al., 2012).

5.5. Lemon balm

The safety and toxicology of lemon balm and its essential oil have been explored *via* several cytotoxic studies. In acute toxicity studies, Stojanović et al. (2019) reported no changes in behavior or organ histopathology in BALB/c mice after lemon balm essential oil was taken orally at doses up to 1 g/kg; sedation, behavior changes and gastrointestinal, and liver and kidney damage occurred at higher doses. The estimated value of the oral LD_{50} was 2.57 g/kg. The data suggest that this oil is only moderately toxic. Sipos et al. (2021) examined an aqueous extract of lemon balm leaves to assess *in vitro* cytotoxicity in immortalized human keratinocytes and the *in vivo* impact on the angiogenesis process and on physiological skin variables in female SKH-1 hairless mice. Lemon balm at different concentrations was not cytotoxic, no vascular toxicity was recorded at a concentration as high as 1 mg/mL, and skin physiology was improved after topical application.

5.6. Lemongrass

Safety and toxicology studies of lemongrass extract and essential oil have been searched *via* cytotoxic and toxicological markers. The viability of murine alveolar macrophages at different doses of 2.5–15 μg of lemongrass extract incubation was investigated and no cytotoxic effect was observed (Tiwari et al., 2010). A 21-day oral toxicity study in male Swiss mice conducted by Costa, Bidinotto, Takahira, Salvadori, Barbisan, and Costa (2011) with lemongrass essential oil at doses of 1, 10, and 100 mg/kg confirmed its safety; the higher dose tested also resulted in blood cholesterol reduction, a presumed beneficial effect.

5.7. Marjoram

The safety of marjoram extracts has been investigated in cytotoxicity studies. Villalva et al. (2018) found that 20 μL of the basolateral fraction of CaCO-2 cells exposed to a marjoram extract enriched in rosmarinic acid as the highest concentration did not decrease cell viability in a human THP-1 macrophage cellular model. Further cytotoxicity studies in the same cellular model using protein formulations containing marjoram extract (10, 50, 100, and 200 μL) showed that cells were viable up to 100 μL volume (Arranz et al., 2019). Besides, marjoram essential oil was investigated in hamsters and no toxic effects were observed after oral treatment (80, 160, and 320 mg/kg) for 14 days (Selim, Abdel Aziz, Mashait, & Warrad, 2013). Thus, the results of experimental studies support the safety of marjoram.

5.8. Peppermint

Researchers have investigated the toxicology of peppermint extracts and essential oil. In one study, the acute oral toxicity of ethanol solution and aqueous extract of *Mentha piperita* leaves were evaluated in male Wistar rats and results showed tolerance for a wide range of doses, with an LD_{50} of the ethanolic and aqueous extracts of 3.7 g/kg and 4.8 g/kg body weight, respectively (Dhanarasu, Selvam, & Al-Shammari, 2016). Other toxicological studies in various rodent models have confirmed the safety and lack of toxicity of peppermint extracts even at relatively high doses, as reviewed by Mahendran and Rahman (2020).

5.9. Rosemary

In a study to assess the acaricidal effects of rosemary, Mossa, Afia, Mohafrash, and Abou-Awad (2019) prepared a nanoformulation of rosemary essential oil and investigated its toxicity in rats at doses of 0.5 g/kg body weight (equivalent to a 30 g dose in humans); no toxic effects or animal mortality were observed. Toxicology studies were conducted in weanling rats fed oil-soluble rosemary extracts to support their authorization as a food additive (Phipps, Lozon, & Baldwin, 2021). Rosemary extracts at different doses (up to 3.8 g/kg body weight) were well tolerated when consumed by rats for 90 days. Liver enlargement and hepatocellular hypertrophy were observed at the highest doses, but were reversible, and microsomal enzyme analyses revealed induction of cytochrome P450 enzymes, indicating that the hepatic effects were adaptive and of no toxicological concern.

5.10. Sage

For the essential oil of sage, Lima et al. (2004) reported lack of toxicity in a culture of murine hepatocytes for concentrations up to 200 nL/mL. Likewise, Radulović, Genčić, Stojanović, Randjelović, Stojanović-Radić, and Stojiljković (2017) showed that sage essential oil was not toxic towards *Artemia salina* (brine shrimps) at different concentrations (5–50 μg/mL). The cytotoxicity of sage extract was assessed in a cell culture assay of RAW 264.7 murine macrophages (De Oliveira et al., 2019). Cells treated with 12.5, 25, and 50 mg/mL concentrations of sage extract disclosed 100% cell viability. In similar experiments with the same cellular model, Brindisi et al. (2021) found that different concentrations of various sage extract isolates shown to reduce NO production did not influence cell viability.

5.11. Thyme

The safety and toxicology of thyme and its essential oil have been studied *via* cytotoxicity studies. De Oliveira et al. (2017) assessed the cytotoxicity of time extracts at concentrations of 25, 50, and 100 mg/mL in cell culture models of murine macrophages (RAW 264.7), human gingival fibroblasts (FMM-1), human breast carcinoma cells (MCF-7), and cervical carcinoma cells (HeLa) and found a dose-dependent decrease in cell viability that was always$<$50%. Liang et al. (2014) investigated the cytotoxicity of thyme essential oil in mouse mammary epithelial cells. The results showed that the observed attenuation of the inflammatory response to LPS stimulation was not related to an eventual cytotoxic effect, as cell viability was not affected by thymol oil at the concentrations used (10, 20, and 40 μg/mL). Using the same *in vitro* assays employed to investigate bay laurel toxicity, Kazeem et al. (2015) showed that thyme exhibited high lethal dose values for both cytotoxicity and phytotoxicity with LD_{50} of 1,000 μg/mL and 1,640 μg/mL, respectively, which supports its safety.

5.12. Concluding remarks

In conclusion, the safety and toxicity of the selected herbal extracts and their essential oils were examined *via* cytotoxic and toxicological

markers. The *in vitro, in vivo*, and (rare) clinical study data available show the safety of the listed herbs. Peppermint, black cumin, marjoram, rosemary, and thyme research suggests that their use is safe. In lemongrass, sage, and fennel studies, no cytotoxic effects were observed in the given ranges. Bay laurel has weak toxicity and lemon balm oil is moderately toxic but is not cytotoxic at the recommended lower doses. Lastly, clove oil is highly toxic at high concentrations; however, the FDA has confirmed the safety of clove for acceptable daily amounts. The toxicology data obtained *via* the *in vivo* studies and (exceptional) clinical trials of some of these herbs/extracts/essential oils is limited and further evaluation is warranted. Furthermore, the influence of the selected herbal extracts and derived essential oils on the metabolism of drugs should also be investigated. The available evidence suggests that all of the medicinal herbs listed are safe for consumption within the recommended ranges.

6. Future perspectives

Medicinal herbs and their essential oils have been used for centuries for different health purposes. Both nutraceutical and pharmaceutical companies are consistently targeting phytochemical extracts, medicinal and aromatic herbs, and essential oils to identify leading bioactive compounds, focusing principally on alternative dietary supplements and drugs. Aromatic herbs as natural products and their essential oils provide a rich source of highly bioactive compounds, principally polyphenols; for the discovery and production of dietary supplements.

Until now, most research concerning the immunomodulatory properties of medicinal herbs and their essential oils has been conducted either *in vitro* (cell culture) or *in vivo* (animal), with some molecular docking studies as well. Therefore, given the preliminary record of safety and lack of toxicity of standard or even high doses of these herbs and derived oils, there is an urgent need to conduct clinical trials. Moreover, the development of drugs from these herbs/essential oils for the treatment of inflammation requires further *in vitro* and *in vivo* tests, the latter both in animals and preferably in humans, to examine pharmacokinetic and pharmacodynamic aspects as well as ranges of therapeutic efficacy. In addition, there are also limited sound studies available for the safety and toxicology of some medicinal herbs and their essential oils. Further investigations regarding in-depth toxicological investigations are warranted to validate their safety.

7. Conclusions

Medicinal herbs have been used for centuries in the form of whole herbal product, extract, oil, powder, capsule, or lotion to enhance health promotion and disease prevention as well as enriching food products for purposes such as flavoring and coloring, among others. Essential oils and extracts of some medicinal herbs and their bioactive compounds have been on the market as nutraceuticals/dietary supplements/herbal products for decades. Therefore, they play important roles in daily life for numerous health purposes, one of which is the enhancement of immunity. The *in vitro* and *in vivo* studies compiled here show that some medicinal herbs and their essential oils possess important immunomodulatory properties and are safe to consume at recommended amounts. Additional well-designed randomized clinical trials are needed to validate the detailed immunomodulatory effects of these herbs.

8. Ethics statement

There are no human clinical trial in this study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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