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Pharmacological effects of volatile oil from chrysanthemum and its associated mechanisms: a review

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Abstract

Volatile oil (VO) is the main chemical component of common plants in Chrysanthemum genus, and it possesses several beneficial pharmacological properties, including bacteriostatic, antioxidant, anti-tumor, anti-inflammatory, antipyretic, analgesic, anti-osteoporotic, antihypertensive, sedative, and hypnotic effects. To date, research on the effective components of Chrysanthemum extract has mainly focused on flavonoids, whereas limited data are available on the chemical constituents and underlying mechanisms of action of the VO components. In this review, the pharmacological activities and mechanisms of VO are comprehensively reviewed with the aim of providing a foundation for further development for medicinal, aromatherapy, and diet therapy applications.

Keywords: Action mechanisms, Chrysanthemum, Pharmacological activity, Volatile oil

Graphical abstract: http://links.lww.com/AHM/A85.

Introduction

Chrysanthemums, characterized by its unique flower color and structure, belong to the Compositae family and are annual or perennial herbs with an over 3,000-year history of cultivation[1,2]. From the perspective of varieties, Chrysanthemum species worldwide are mainly divided into Chinese, Japanese, and European groups. The plant has been used as a food ingredient, additive, beverage, and medicine in several countries since ancient times, particularly in China and Korea[3,4]. In China, Japan, Vietnam, and other Eastern countries, boiled dried Chrysanthemum has been used to prepare herbal teas to relieve fever and treat eye diseases for over 2,000 years[5]. The medicinal efficacy of Chrysanthemum was first recorded in *Shennong Herbal Classic* (神农本草经) in China, with reported potency for the treatment of headaches and vertigo, among other symptoms[6]. Chrysanthemum is included in the Pharmacopoeia of the People's Republic of China (2020 Edition) as a medicinal food plant and is classified into five medicinal varieties: Chrysanthemum morifolium (Bo), Chuzhou Chrysanthemum (Chu), Florist Chrysanthemum (Gong), Chrysanthemum morifolium (Hang), and Huaiqing Chrysanthemum (Huai), depending on the growing regions[7].

Modern pharmacological studies have identified flavonoids, volatile oil (VO), organic acids, and triterpenoids as the major components of Chrysanthemum. To date, studies have predominantly focused on the VO from *Chrysanthemum morifolium* Ramat. and *Chrysanthemum indicum* L. in China, which are recorded in the Chinese Pharmacopoeia[7]. The composition of Chrysanthemum VO is complex and includes monoterpenes, sesquiterpenes, and oxygen-containing derivatives[8,9]. However, current research mainly involves the optimization of the VO extraction process, with limited attention to the pharmacological effects and mechanisms of action.

In this report, the pharmacological properties and underlying mechanisms of Chrysanthemum VO are comprehensively reviewed to provide a basis for exploring and developing its clinical applications. The word cloud describing the main pharmacological effects of Chrysanthemum VO is presented in Figure 1.

The following retrieval and summary methods were used: (1) initial search based on the main keywords,

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Jing Zhang and Weiqiang Su contributed equally to this work.

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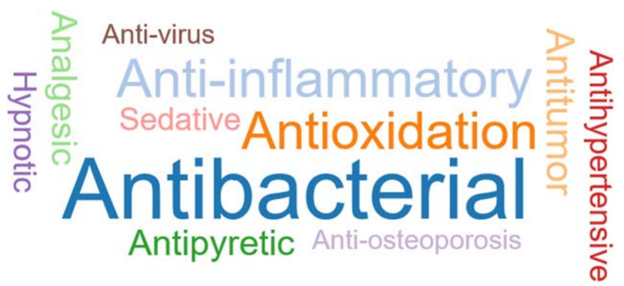

Figure 1. Pharmacological actions of Chrysanthemum VO. The common effects of Chrysanthemum VO are presented as a "word cloud," whereby the size of each pharmacological activity is positively correlated with frequency of its reports in literature. VO: Volatile oil.

specifically, "medicinal plant" "volatile oil" "chrysanthemum" "volatile oil components" and "pharmacological effect" in PubMed, Web of Science, ScienceDirect, and other databases; (2) preliminary screening of the literature based on title, keywords, and guidelines; (3) addition of recent research progress and new references from the original literature; and (4) summary and collation of the available literature.

Pharmacological effects and underlying mechanisms

Antimicrobial effect

Chrysanthemum VO contains a mixture of terpenoids, phenols, alcohols, and other chemical components that exert significant antibacterial effects against several pathogenic microorganisms, such as *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus mutans*, *Pseudomonas aeruginosa*, and *Listeria monocytogenes*[9–11]. Common varieties of Chrysanthemum VO and their active antimicrobial components are presented in Table 1[11–13].

The active components of Chrysanthemum VOs differ depending on the origin of the plant. The antibacterial effect is not attributed to individual components and mechanisms but may be the result of multi-component synergy, multiple pathways, and multi-target actions in cells[14]. Figure 2 depicts the sites of action and mechanisms of VO components in bacterial cells. Notably, many of these mechanisms are affected by multiple pathways[15,16].

Destruction of cellular structure integrity

The integrity of the cell structure is the premise for maintaining the normal physiological activities of microorganisms. Owing to their hydrophobic nature, VO and their components are proposed to be distributed in the microbial cell membrane, inducing destruction of the cellular structure, increased membrane permeability, and outflow of critical molecules from the cell, triggering internal disorder, disruption of the steady-state balance of bacterial cells, and ultimately, death of microorganisms[17]. A previous study reported that Chrysanthemum VO inhibited the growth of *Phytophthora nicotianae* and exerted a bacteriostatic effect by increasing cell membrane permeability, destroying the structure of the mycelium, and causing cell rupture[18]. Another report on the bacteriostatic activity of Chrysanthemum VO against *Listeria monocytogenes* consistently demonstrated the destruction of the bacterial cell membrane and increased permeability, leading to the leakage of important physiological molecules, such as deoxyribonucleic acid (DNA), protein, and adenosine triphosphate (ATP). Subsequently, the intracellular content is significantly reduced and cell surface conductivity and adsorption rates increase, eventually leading to bacterial death[10].

Effects on cellular nucleic acid metabolism and protein synthesis

VO inhibits the expression of nucleic acid metabolism genes and promotes cell death by blocking the biosynthesis of microbial nucleic acids, proteins, and peptidoglycans[19]. DNA is a carrier of genetic information that is critical for the synthesis and genetic processes of microbial cells. DNA topoisomerases are essential enzymes involved in DNA replication, transcription, and translation, and damage to these enzymes affects the normal replication, growth, and reproduction of genetic material[20]. The active compound thymol reduces bacterial adhesion and virulence by downregulating a gene encoding the outer membrane protein of *Acinetobacter baumannii*[21]. The VO of Chu Chrysanthemum inhibits the activities of intracellular enzymes such as adenosine triphosphatase (ATPase) and alkaline phosphatase (ALP), which are crucial for bacterial growth. It also inhibits topoisomerases I and II, leading to a subsequent increase in the proportion of supercoiled DNA, which affects nucleic acid metabolism and eventually triggers bacterial death[22].

Inhibition of microbial energy and respiratory metabolism

ATP is the direct source of energy for all life processes. Upon inhibition of ATP synthase, metabolism is significantly affected, leading to the death of microorganisms[23]. Thymol and eugenol induced the acidification of the intracellular environment of *Candida* by inhibiting the activity of proton-translocating ATPases, resulting in bacterial cell death[24]. Similarly, Chrysanthemum VO inhibited the respiratory metabolism of cells of *Listeria monocytogenes* through the inhibitory effects of iodoacetic acid, malonic acid, and trisodium phosphate dodecahydrate on the activity of enzymes in the glycolytic pathway[10]. Collectively, these findings indicate that Chrysanthemum VO promotes intracellular ion loss by destroying microbial cell membranes, thereby disrupting the balance of intracellular and extracellular ATP and exerting a bacteriostatic effect.

Other effects

VO from medicinal plants can induce the coagulation of the microbial cytoplasm, resulting in a bacteriostatic effect. The cytoplasm is the hub for all physiological activities. Upon solidification, the metabolism and chemical reactions of cells cannot proceed normally, eventually causing microbial death[25]. Carvacrol inhibited bacterial quorum sensing to decrease bacterial virulence and induces bacteriostasis by inhibiting LasI synthase activity, with a concomitant reduction in LasR protein expression, biofilm formation, swarming motility, and a

Table 1

Main active antibacterial components of VO from different varieties of Chrysanthemum

Main antibacterial active ingredients	Chrysanthemum species			
	***Chrysanthemum morifolium* Ramat.**	***Chrysanthemum indicum* L.**	***Chrysanthemum boreale* Makino**	***Chrysanthemum zawadskii* Herbich**
Monoterpene hydrocarbons				
Pinene	√	√	√	√
Terpinene	√	√	√	√
Camphene		√	√	√
Thujene		√	√	√
Phellandrene				
Myrcene			√	√
Limonene	√	√	√	
Oxygenated monoterpenes				
Camphor	√	√	√	√
Borneol	√	√	√	√
Thujone	√	√	√	√
Linalool		√	√	
Carvacrol		√	√	
Terpinen-4-ol		√	√	√
Terpineol	√	√	√	
Myrtenol	√	√	√	√
Thymol		√	√	√
Cineole	√	√	√	√
Bornyl acetate	√	√	√	√
Sesquiterpenes hydrocarbons				
Caryophyllene	√	√	√	√
Curcumene	√	√	√	
Guaiene	√		√	
Elemene	√			√
â-Sesquiphellandrene			√	√
Oxygenated sesquiterpenes				
Nerolidol	√		√	√
Eudesmol	√	√		
Caryophyllene oxide	√	√	√	

VO: Volatile oil.

The overall composition and VO content in the same variety of Chrysanthemum can vary depending on the origin, processing method, and detection method.

subsequent decrease in acyl-homoserine lactone production in *Pseudomonas aeruginosa*[26].

Anti-inflammatory effect

Inflammation is an essential biological mechanism that represents the defensive response of an organism to stimulation by various inflammatory factors[27]. Luteolin, apigenin, linarin, and other flavonoids present in Chrysanthemum extracts exhibit anti-inflammatory properties. The significant anti-inflammatory activities of terpenoids, esters, phenols, and other compounds in VO have also been confirmed, which mainly regulate the synthesis and release of cellular inflammatory factors and block signaling pathways[27], as depicted in Figure 3.

Inhibition of pro-inflammatory factor production

Cytokines are low-molecular-weight soluble proteins that are synthesized and secreted by cells such as lymphocytes, macrophages, and epithelial cells. They have diverse biological functions and exert both anti-inflammatory and pro-inflammatory effects[28,29]. Pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8), enhance the inflammatory reaction and immunity[28]. VO inhibits the production of inflammatory factors and the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) to block the production of related mediators, thus exerting an anti-inflammatory effect. In addition, iNOS and COX-2 are modulated through nuclear factor-κB (NF-κB) activation to regulate

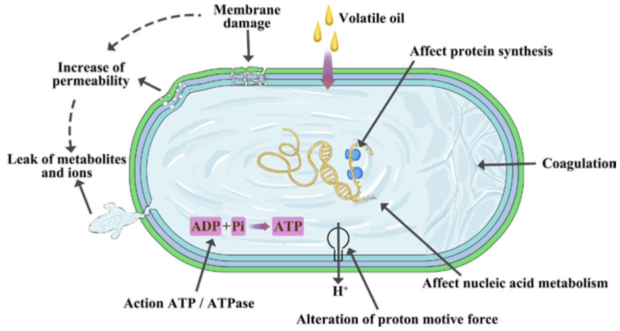

Figure 2. Mechanisms underlying the antibacterial effects of Chrysanthemum VO. ADP: Adenosine diphosphate; ATP: Adenosine triphosphate; ATPase: Adenosine triphosphatase; Pi: Inorganic phosphate; VO: Volatile oil.

the production of prostaglandin E_2 (PGE_2) and nitric oxide (NO)[30]. Previous mechanistic studies have shown that specific sesquiterpenoids in Chrysanthemum exhibited significant anti-inflammatory activity by inhibiting NO production in RAW 264.7 cells stimulated with lipopolysaccharide (LPS)[31,32]. Parthenolide (PTL) was reported to inhibit the expression of inflammatory cytokines (IL-1β, IL-6, IL-8, IL-12p40, IL-18, TNF-α, and NO) in LPS-induced THP-1 cells in a dose-dependent manner, indicating activity against LPS-mediated pro-inflammatory responses in cells[33]. In LPS-stimulated RAW264.7 macrophages *in vitro*, handelin from *Chrysanthemum boreale* not only inhibited the induction of the pro-inflammatory cytokines (IL-1β and TNF-α), but also inhibited PGE_2 and NO produced by the cells in a concentration-dependent manner (20 μM handelin inhibited NO production by >84% while the inhibition rate at 40 μM was 98%). Moreover, this inhibitory effect was related to the downregulation of mRNA and protein expression of COX-2 and iNOS[34].

Blockage of signaling pathways

VO of medicinal plants exerts anti-inflammatory effects by the blockade of NF-κB and mitogen-activated protein kinases (MAPK) signaling pathways.

Upon stimulation of cells, the stimulatory agent binds to the receptor protein on the membrane and activates the inhibitor of NF-κB (IκB) kinase (IKK). Subsequently, IκB undergoes phosphorylation, thereby releasing NF-κB that translocates to the nucleus and interacts with specific DNA sequences, inducing pro-inflammatory factors to enhance the expression of secondary inflammatory mediator enzymes and ultimately causing inflammation[35,36]. VO can inhibit the release of NF-κB by blocking specific pathways to reduce the release of inflammatory mediators and associated gene expression. Bornyl acetate, the main VO constituent in some traditional Chinese herbs, exerts anti-inflammatory effects *via* decreasing the transcriptional activity of NF-κB in a concentration-dependent manner and blocking p65 nuclear translocation induced by the oxidized form of low-density lipoprotein (LDL)-cholesterol[37].

MAPK is a key signaling pathway involved in the stress response. Upon stimulation of cells by the appropriate mediators, MAPK kinase and MAPK kinase are activated, which in turn activates MAPK, which acts on downstream molecules to regulate specific genes, thereby modulating inflammation and other reactions[38,39]. Chrysanthemum VO suppresses the activity of extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK), and p38 in the MAPK pathway. The anti-inflammatory mechanism of the PTL component involves inhibition of toll-like receptor 4 (TLR4)-mediated MAPK and NF-κB pathways through dose-dependent suppression of LPS-induced upregulation of phosphorylated ERK 1/2, JNK, p38, NF-κB, p65, IκBα and expression of iNOS, TLR4, and TNF receptor–associated factor 6[33]. Additionally, research has revealed that handelin ameliorated inflammation by downregulating NF-κB and blocking the ERK and JNK signaling pathways in MAPK[34]. In addition, the anti-inflammatory activity of the sesquiterpene compound chrysanthemulide A, a constituent of the herb *Chrysanthemum indicum*, appears to be mediated *via* the suppression of the LPS-induced NF-κB pathway and downregulation of MAPK activation[40].

Antioxidant activity

Oxidative stress is a known pathological mechanism in many diseases, and the inhibition of this process plays a crucial role in preventing and curing diseases. Chrysanthemum has been reported to protect against liver damage *via* antioxidant effects[41]. Chrysanthemum VO are rich in phenols and other compounds with significant antioxidant activity, particularly thymol, carvacrol, and eugenol; therefore, they have potential utility as natural antioxidants[42]. VO can be incorporated as a natural preservative into various food and pharmaceutical preparations. The antioxidant activity of VO is mainly exerted through the mechanisms described in the next sections.

Blockage of the free radical chain reaction

VO from medicinal plants can play an antioxidant role by blocking free radical chain reactions, including free radical scavenging and chelation with metal ions, as depicted in Figure 4[43].

The phenol compounds in Chrysanthemum VO, such as eugenol, thymol, and carvacrol, can provide active H-atom to react with the free substrate (ROO) faster than substrate RH to generate stable substances of non-free substrate ROOH and antioxidant free radicals, thereby interrupting the free radical chain reaction to exert antioxidant effect[44,45]. By preventing the generation of free radicals, thymol in VO reduced intracellular oxidative stress in a dose-dependent manner, exerted anti-cholinesterase activity, and improved the viability of neuronal PC-12 cells[46].

Research has also shown that Chrysanthemum VO had a strong antioxidant capacity in 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydroxyl radical scavenging, and superoxide radical scavenging experiments, with 50% inhibitory concentration (IC_{50}) values of 2.59, 2.89, and 5.92 mg/mL, respectively. An explanation for this activity, in addition to its role as a pro-oxidant, can be found in the synergistic effect between all VO components[12]. Compounds

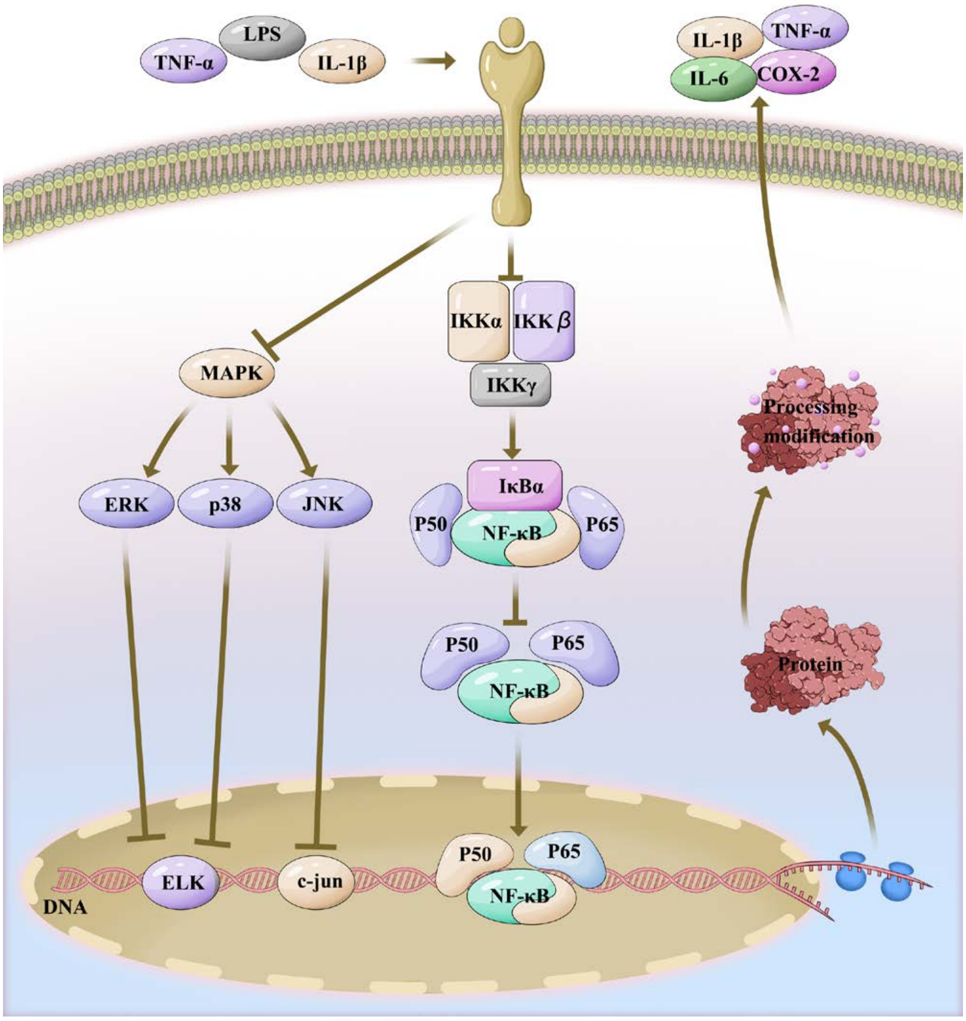

Figure 3. Signaling pathways underlying the anti-inflammatory effects of Chrysanthemum VO. COX: Cyclooxygenase-2; ELK: Transcription factor ELK; ERK: Extracellular signal–regulated kinases; IKK: NF-κB (IκB) kinase; IL: Interleukin; c-jun JNK: c-Jun N-terminal kinase; LPS: Lipopolysaccharide; MAPK: Mitogen-activated protein kinases; NF-κB: Nuclear factor-κB; P50: NF-κB p50 subunit; P65: NF-κB p65 subunit; TNF-α: Tumor necrosis factor-α; VO: Volatile oil.

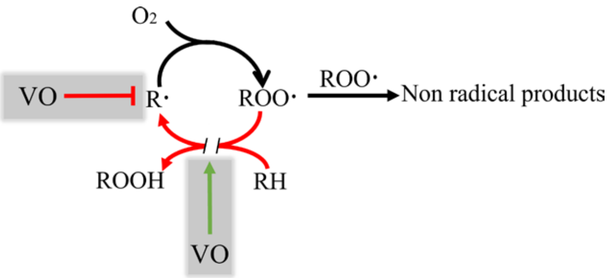

Figure 4. Effect of antioxidants in Chrysanthemum VO on free radical chain reaction. VO: Volatile oil.

including α-terpinene, β-terpinene, β-terpinolene, 1,8-cineole, and terpinen-4-ol are considered to contribute to the antioxidant effect of VO[47]. Moreover, VO obtained at different growth stages (vegetative, pre-flowering, and full-flowering stages) of *Chrysanthemum boreale* Makino displayed varying degrees of antioxidant activity, which promoted the DPPH and azinobis-(3-ethylvensothiaxoline-6-sulfonic acid) scavenging of cells. Eugenol from *Chrysanthemum boreale* Makino VO exhibited the highest scavenging efficiency, compared with that of other components, at concentration from 0.1 to 20 μg/mL[48].

Involvement in other antioxidant pathways

Various bioactive components in Chrysanthemum VO can improve the antioxidant defense ability of the body by inhibiting lipid peroxidation or regulating antioxidant enzyme levels by participating in other related antioxidant stress signaling pathways[43], such as the activation of nuclear factor erythroid 2–related factor 2 (Nrf2)–related antioxidant pathways[49]. According to a recent study, germacrane-type sesquiterpenoids in Chrysanthemum can promote the dissociation and translocation of Nrf2 from Kelch-like ECH-associated protein 1 (Keap1) to the nucleus by anchoring to the Kelch domain-binding site of Keap1, thereby reducing the accumulation of reactive oxygen species (ROS) and increasing glutathione and heme oxygenase-1 levels and superoxide dismutase activity, thereby protecting the liver against oxidative damage[50].

Anti-tumor effect

Chrysanthemum has a long history of clinical applications for therapeutic purposes, such as killing pathogenic microorganisms, improving immunity, and treating malignant tumors[51,52]. Herbal medicines with cold and cool in nature are generally used for tumor management[53,54]. Recent research has identified a variety of effective chemical components in Chrysanthemum VO, such as PTL, β-elemene, and 1,8-cineole, that effectively exert anti-tumor effects against several cancer cell types. The therapeutic effects and mechanisms of action of the active ingredients of VO in different cancer types are shown in Table 2.

Parthenolide

PTL is a natural sesquiterpene lactone bioactive component extracted from the traditional medicinal plants of Asteraceae, such as *Chrysanthemum parthenium* L[81]. It exerts anti-proliferative and pro-apoptotic effects in various malignant tumor types, including leukemia, prostate cancer, and osteosarcoma, both *in vitro* and in animal models, supporting its potential as a first-line clinical anticancer drug[80–82]. Moreover, the synergistic effects of the interactions of several drugs with their targets, combined with the actions of PTL, have been reported to effectively inhibit the malignant proliferation of cancer cells[78]. Data from the available literature suggest that PTL regulates related signaling pathways, such as signal transducer and activator of transcription 3 (STAT3), phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), mitogen extracellular signal-regulated kinase (MEK)/ERK, Wnt (wingless)/β-catenin, pyruvate kinase M2 (PKM2)-STAT3, and NF-κB, to block the cancer cell cycle and induce apoptosis[79]. Subcutaneous injection or oral administration of PTL suppressed the production of IL-8 and vascular endothelial growth factor an OUR-10 nude mouse xenograft model and reduced nuclear localization of NF-κB and its phosphorylated form, causing decreased expression of metalloproteinase-9, anti-apoptotic factor Bcl-xL, and COX-2[83]. Collectively, these findings indicate that PTL inhibits the growth of renal cancer cells by blocking NF-κB activity.

β-Elemene

β-Elemene, a non-cytotoxic anti-tumor drug developed by China with broad-spectrum anti-tumor properties, is also abundant in Chrysanthemum VO. Elemene Injection (approval number H20110114), Elemene Emulsion Injection (approval number H10960114), and Elemene Oral Emulsion (approval number H20010337) have been approved by the National Medical Products Administration in China for the treatment of liver, lung, esophageal, and other cancer types. As a non-cytotoxic drug, β-elemene exerts effects against different tumor cell types *via* multiple mechanisms. In general, the molecular mechanisms of β-elemene include blockage of the cell proliferation cycle, apoptosis induction, inhibition of tumor growth and metastasis, enhancement of tumor cell immunogenicity, and reversal of multidrug resistance[69]. In addition, multiple signaling pathways and enzymes or proteins (including NF-κB, MAPK, PI3K-Akt-mammalian target of rapamycin (mTOR), B-cell lymphoma 2 (Bcl-2) protein family and caspases, and Wnt/β-catenin) are involved[70]. Research on the combination of β-elemene and 5-fluorouracil showed that β-elemene reversed the resistance of HCT116p53 to 5-fluorouracil by inducing apoptosis, autophagy, and cyclin D3–dependent cell cycle arrest[84].

1,8-Cineole

1,8-Cineole is a highly selective cyclic monoterpene compound with potential anti-tumor activity against human colon, skin, liver, ovarian, osteosarcoma, and breast cancer cells *in vitro* and *in vivo*[74]. Numerous preclinical efficacy studies have provided extensive evidence that 1,8-cineole regulates related signaling pathways and enzymes or proteins, such as tumor suppressor protein p53, PI3K/Akt, aryl hydrocarbon receptor (AHR)/cellular Src (c-Src)/epidermal growth factor receptor (EGFR), rapidly accelerated fibrosarcoma (RAF)-MEK1/2-ERK1/2, Bcl-2 protein family, and adenine monophosphate-activated protein kinase (AMPK), to destroy mitochondrial integrity, inhibit tumor cell proliferation and induce apoptosis[85–87].

1,8-Cineole has also been shown to promote G0/G1 cycle arrest in HepG2 cells by inhibiting cell proliferation. Furthermore, when cells were incubated with1,8-cineole at a concentration of 8 mM, the level of cyclin-dependent kinase 4/6 decreased, ROS production significantly increased, and ERK phosphorylation (p-ERK) and p-p38 increased by 2- and 5.7-fold, respectively. Although the p-Akt was higher, the p-p70S6K (p70 ribosomal protein S6 kinase, mTOR downstream target) was decreased by 57%, and AMPK was activated, which induced the senescence of HepG2 cells to anti-senescence compounds. Therefore, the combination of 1,8-cineole and these compounds synergistically inhibited tumor cell viability and induced tumor cell apoptosis[88].

Other pharmacological effects and mechanisms

Anti-pyretic and analgesic activity

Fever is usually caused by the interaction between pyrogens and the organum vasculosum lamina terminalis, which leads to the upregulation of body temperature by the hypothalamic thermoregulation center, resulting in fever[89]. Pain is triggered by the formation and release of pain-inducing substances, such as histamine, dopamine (DA), 5-hydroxytryptamine (5-HT), and prostaglandins (PG), at the site of inflammation or injury, which act on pain receptors[90,91]. The mechanism underlying antipyretic and analgesic activity is similar to that of anti-inflammatory action, which involves blockage or reduction of NO, PGE_2, and other related mediators through inhibiting expression of COX-2 and iNOS or regulation of related signaling pathways, in particular NF-κB[92,93]. In studies on the antipyretic effect and underlying mechanisms of VO from *Chrysanthemum morifolium* using a New Zealand rabbit model of endotoxin-induced fever, the high-dose group (0.096 mL/kg VO) showed reduced norepinephrine (NE) and DA contents from 0.17 and 0.09 μg/mg to 0.11 and 0.05 μg/mg, respectively, compared with the model group, while the 5-HT content increased from 1.59 to 2.40 ng/mg, inferring that the antipyretic effect of VO is related to alterations in the 5-HT, DA, and NE contents[94].

Table 2

Main anti-tumor components and mechanisms of Chrysanthemum VO

Active component	Cancer type	Mechanism								Reference
		Induces cell autophagy	Induces oxidative stress	Inhibits cell proliferation	Blocks cell cycle	Induces apoptosis	Induces cell DNA damage	Inhibits migration and invasion	Induces mitochondrial structural change or apoptosis	
Borneol	Liver cancer, glioma		√		√	√	√		√	[55,56]
Geraniol	Breast cancer, colon cancer, kidney cancer, liver cancer, lung cancer, oral cancer, pancreatic carcinoma, prostate cancer, skin cancer	√		√	√	√	√	√	√	[57,58]
Thujone	Human placental choriocarcinoma, malignant melanoma, ovarian cancer	√				√			√	[59–61]
Limonene	Bladder cancer, breast cancer, colon cancer, gastric cancer, leukemia, liver cancer, lung cancer, lymphoma, neuroblastoma, pancreatic cancer, prostate cancer, skin cancer	√	√	√	√	√	√	√	√	[62,63]
Carvacrol	Breast cancer, cervical cancer, colon cancer, gastric cancer, leukemia, liver cancer, lung cancer, melanoma, neuroblastoma, oral cancer, prostate cancer, human glioblastoma, human tongue squamous cell carcinoma		√	√	√	√	√	√	√	[64,65]
α-Pinene	Cervical cancer, gastric cancer, liver cancer, ovarian cancer			√	√	√	√			[66,67]
Thymol	Bladder cancer, bone cancer, breast cancer, cervical cancer, colon cancer, colorectal adenocarcinoma, gastric cancer, glioblastoma, liver cancer, lung cancer, neuroblastoma, prostate cancer		√	√	√	√	√	√	√	[64–68]
β-Elemene	Bladder cancer, bone metastasis, brain cancer, breast cancer, cervical cancer, esophageal cancer, gastric cancer, liver cancer, lung cancer, malignant glioma, nasopharyngeal cancer, ovarian cancer, prostate cancer	√		√	√	√		√		[69,70]
β-Caryophyllene	Breast cancer, cervical cancer, colon cancer, gastric cancer, leukemia, liver cancer, lung cancer, ovarian cancer, prostate cancer		√	√	√	√	√		√	[71–73]
1,8-Cineole	Breast cancer, colon cancer, leukemia, liver cancer, oral cancer, ovarian cancer, skin cancer,		√	√	√	√		√	√	[74]
α-Bisabolol	Breast cancer, endometrial cancer, glioblastoma cells, hepatocellular carcinoma, non-small cell lung cancer, leukemia cells, liver cancer, pancreatic cancer	√		√	√	√		√	√	[75–77]
PTL	Breast cancer, colorectal cancer, gastric cancer, leukemia, liver cancer, lung cancer, malignant glioma, melanoma, prostate cancer, thyroid cancer	√	√	√	√	√		√	√	[78–80]

PTL: Parthenolide.

Anti-hypertensive activity

Herbal medicine protects against hypertension mainly through the inhibition of sympathetic nerve activity, blockage of the calcium channel, diuresis, hypotension, suppression of the pathological processes in the renin-angiotensin system, improvement of vascular endothelial function and insulin resistance, and effects on cardiac hemodynamics and hemorheology or synergistic effects of multiple pathways of hypotension[95,96]. 1,8-Cineole from VO inhibited calcium ion influx in cells with concomitant relaxation of isolated arteries and reduction of aortic pressure[97], while carvacrol increased cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels by inhibiting various phosphodiesterases, exerting an endothelium-independent vasodilatory effect[98]. The systolic blood pressure and heart rate of subjects decreased after inhalation of VO; in addition, brain waves θ and α increased in the relaxed brain state while β and γ waves decreased during activity, indicating that VO from *Chrysanthemum indicum* helps to reduce blood pressure and relax the body and mental state[99]. Chrysanthemum extract, rich in polyphenols, reduces renovascular hypertension. Through inhibiting the expression of hypoxia-inducible factor-1α and regulating carnitine palmitoyltransferase-1a, pyruvate dehydrogenase kinase-4, and glucose transporter-4, Chrysanthemum extract improved myocardial energy metabolism, leading to the attenuation of hypertension-induced myocardial hypertrophy in rats[100].

Sedative and hypnotic effects

Insomnia is a disorder that leads to difficulty falling asleep or maintaining sleep, poor sleep quality, and shortened total sleep time as the main manifestations. The pathogenesis of insomnia is mainly associated with central neurotransmitters, inflammatory factors, and the hypothalamus-pituitary-adrenal axis[101,102]. Sleep deficiency reduces the quality of life and leads to mental health problems, especially anxiety and depression[103]. A number of clinical and pharmacological studies have validated the utility of VO in medicinal plants administered *via* inhalation, oral administration, or aromatherapy for sedation and hypnosis, and relief of anxiety and depression[104]. Studies have indicated that the ethanolic extract of *Chrysanthemum morifolium* can regulate the expression of glutamic acid decarboxylase and enhance pentobarbital-induced sleep behavior, which may be caused by the activation of Cl^- channels[105,106]. Chrysanthemum VO may participate in sleep regulation mechanisms to improve sleep by regulating the levels of 5-HT, NE, or TNF-α to exhibit sedative and hypnotic effects[107]. However, the underlying mechanisms have not yet been elucidated.

Anti-osteoporotic activity

Osteoporosis is a systemic metabolic bone disease characterized by decreased bone mass, destruction of bone tissue microstructure, and an increased risk of bone fragility and fracture[108]. Herbal medicines exert anti-osteoporotic effects through regulation of Wnt/β-catenin, bone morphogenetic protein (BMP)/Smad, MAPK pathways and the receptor activator of NF-κB ligand (RANKL)/osteoprotegerin system (OPG)[109]. VOs are herbal components that effectively regulate bone metabolism and prevent osteoporosis[110]. Monoterpenes (borneol, camphor, menthol, and thymol) isolated from VOs inhibit bone resorption *in vivo* by directly affecting osteoclast formation in hematopoietic cells[111]. The growth level of osteoblasts treated with 10 μg/mL VO of *Chrysanthemum indicum* L. increased to 111%, alkaline phosphatase activity increased to 109%, collagen synthesis level reached 114%, and mineralization increased to 118% compared with the control group, indicating that VO promotes collagen synthesis, activates alkaline phosphatase activity, and accelerates calcium deposition of MC3T3-E1 cells, supporting its utility as a pharmacological agent for osteoporosis[112].

Anti-viral effects

Terpenoids, phenols, aldehydes, and their derivatives in plant VO exert inhibitory effects during different stages of the viral replication cycle by inactivating the virus, protecting host cells, inhibiting viral adsorption by host cells, controlling the proliferation and spread of the virus, and regulating immunity[113,114]. 1,8-Cineole directly combines with and inactivates free viruses by binding to viral proteins involved in the entry and penetration of host cells, thus effectively preventing viral infections[115]. Carvacrol attenuated the excessive immune response induced by the influenza A virus by suppressing viral replication and recognizing TLR/retinoic acid-induced gene I-like receptor (RLR) patterns[116]. β-Caryophyllene improved damage induced by toxic Newcastle disease virus in birds by suppressing viral replication and regulating immunity to increase the level of interferon α (a signaling cytokine), exerting optimal therapeutic effects before or during infection[117]. Certain sesquiterpenoids in Chrysanthemum VO exhibit selective anti-viral activities. Three sesquiterpenoids (chrysanthemumin B, 6,8-cycloeudesm-4(15)-en-1-ol, and 1β-hydroxy-4(15),5E,10(14)-germacratriene) isolated from *Chrysanthemum indicum* inhibited the replication of porcine epidemic diarrhea virus in a dose-dependent manner (concentration range: 20–90 μM). Moreover, chrysanthemumin B had an inhibitory effect on the synthesis of viral nucleocapsid in a dose-dependent manner and spike protein at 80, 40, 20, and 10 μM[118].

Prospects

Novel VO delivery systems

Chrysanthemum VO exhibits a variety of biological activities and pharmacological effects and has been widely investigated and used in the fields of medicine, food, agriculture, and skin care. Notably, because of the volatility, instability, and hydrophobicity of VO and its susceptibility to enzymatic reactions, its utility is limited[119]. The use of novel delivery systems (NDS) for encapsulating VOs can overcome these drawbacks. This is a promising strategy for the development and innovation of Chrysanthemum VO application.

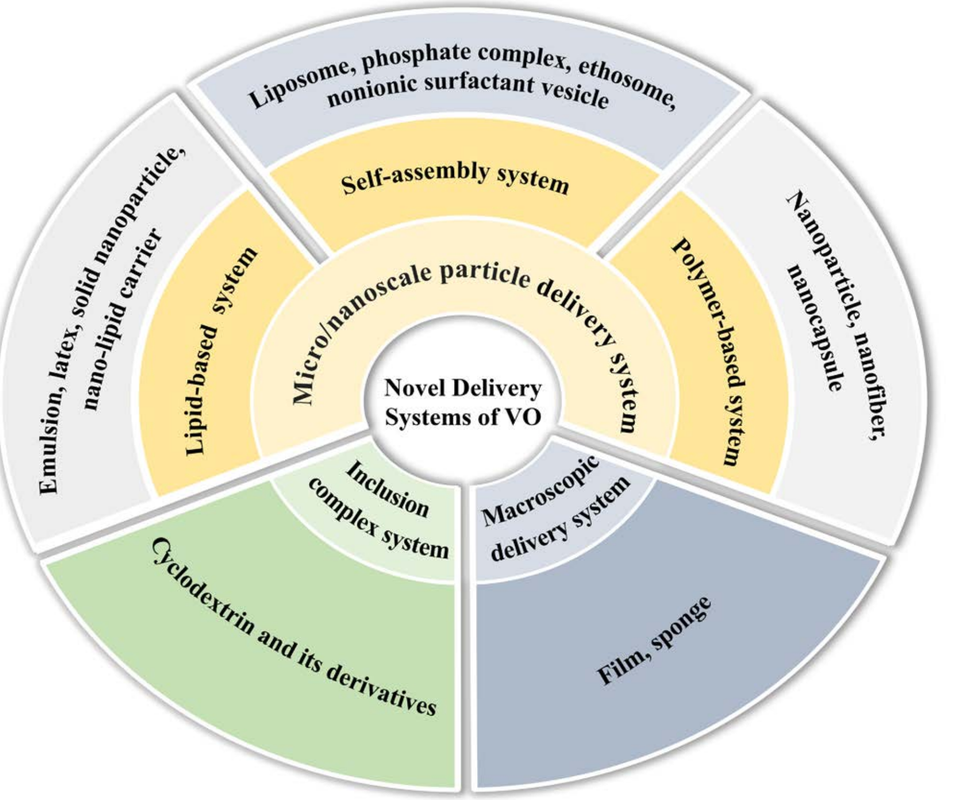

Figure 5. Novel delivery systems designed for VO. VO: Volatile oil.

The encapsulation of VO is commonly defined as a technical means and method strategy to encapsulate VO in “inert” materials with special structure to improve the stability and bioavailability of VO[120]. Based on the different encapsulation materials and techniques, novel delivery systems can be mainly divided into inclusion complexes, micro/nanoscale particles, and macroscopic delivery systems[121]. Figure 5 shows the NDS used to improve the stability and bioavailability of the VO.

Among them, cyclodextrins, liposomes, and nanoparticles have been widely explored as potential delivery systems for VO. Cyclodextrin inclusion complexes have polar hydroxyl groups on the outside of the ring and nonpolar hydrogen and ethereal oxygen on the inside of the ring, forming hydrophobic cavities that can encapsulate VO within the cavity and improve its stability[122]. Qin et al.[123] have demonstrated that the combination of Chrysanthemum VO with β-cyclodextrin can reduce the instability and photosensitivity of VO, and effectively disguise the bad odor of VO, whereas the properties and main components of VO remain unchanged. Moreover, researchers have used chitosan and pectin to modify Chrysanthemum VO liposomes to form more stable Chrysanthemum VO triple-layer liposomes, which showed better antibacterial activity against *Campylobacter jejuni* in chickens without affecting their quality[124]. Moreover, nanotechnology for VO delivery, which is characterized by improved cellular uptake, controlled release, and precise targeting, is a current focus of interest[125,126]. Compared to traditional emulsions, nanoemulsions are stabler because of their higher surface-to-volume ratio, which can be used as a promising antibacterial delivery method to enhance the stability of VO, organ and cellular targeting, and antibacterial efficacy[127].

Pharmacological effects of VO can be further enhanced by (1) achieving targeted drug delivery and controlled drug release to enhance bioavailability and efficiency, (2) preventing hydrolysis and oxidation to improve the chemical stability, and (3) reducing toxicity and volatility[128]. However, studies on the NDS of Chrysanthemum VO are still in the preliminary exploratory stage, particularly for nanodelivery systems and clinical availability may take some time.

VO mechanisms of action

Since Chrysanthemum VO has complex components that act on pathological tissues through multiple pathways and targets, study of the mechanisms of the pharmacological effects of Chrysanthemum VO is challenging. The pharmacological mechanisms of the sedative, hypnotic, hypotensive, and analgesic effects remain the focus.

To develop more feasible patented products for use in the medical, food, and agricultural fields, the mechanisms of action and pharmacological toxicity of VO should be comprehensively investigated, along with further *in vivo* studies and innovations in the formula encapsulation of VO, with the aim of providing reliable data to ensure safe and effective usage.

Conclusions

Chrysanthemum is a medicinal and edible herb containing abundant VO. Over the years, the utility of

Chrysanthemum VO as a therapeutic agent with great potential has been gradually recognized by researchers in various fields, not only in clinical and cosmetic skin care as a potential natural bacteriostatic or antioxidant agent and in other therapeutic drugs[129,130], but also as a potential natural antiseptic additive and biodegradable food packaging in the food industry[131]. The VO extract is also a natural biological insecticide that is commonly used in agricultural pest control[132].

This review focuses on the pharmacological effects of Chrysanthemum VO and their mechanisms of action. Recent advances in effective delivery by NDS are also summarized to shed light on further applications of VO as an important resource for medicinal treatment, aromatherapy, and dietary therapeutic applications.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Jing Zhang, Xiang Li, and Ming Yang conceived and designed the review. Weiqiang Su, Yao He, Ying Luo, Nina Filipczak, Shijuan Yan, Ming Yang, and Anping Wan performed the research. Jing Zhang and Weiqiang Su drafted the manuscript. Xiang Li and Nina Filipczak revised the manuscript. All authors read and approved the final manuscript.

Ethical approval of studies and informed consent

Not applicable.

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None.

Data availability

All data generated or analyzed during this study are included in this published article.

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