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Health aspects of geraniol as a main bioactive compound of *Rosa damascena Mill*: a systematic review

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Abstract

Background: Geraniol (GE), as secondary metabolites of plant and natural bioactive essential oils is one of the major compounds of *Rosa damascena Mill* and widely used as fragrance/flavor in the food industry. *Rosa damascena Mill* and geraniol have numerous health benefits for human consumption. Currently, there is no single article that extensively covers the complete range of beneficial effects of GE that could improve knowledge in this category.

Objective: The purpose of this study was to provide a comprehensive review of all published specific articles about beneficial properties of GE, as a monoterpene component of medicinal plants.

Methods: Data were selected from Scopus, Clarivate Web Of Science™, Embase, ScienceDirect and PubMed databases from 1940-2019 by identifying keywords and creating complex searches.

Results: Based on the search results, GE identified as a natural compound having insecticidal and repellent activities. GE introduces a new class of cancer chemopreventive agents due to its citronellol and trans-geraniol. Other functional properties such as antibacterial, antifungal, antioxidant and anti-inflammatory of GE have also been found.

Conclusion: Overall, this approach has been a systematic literature review to provide an effective strategy for rapidly evaluating research results. This study suggests that the GE and *Rosa damascena Mill* have multiple health benefits and they are recommended for their therapeutic effects.

Keywords: Geraniol; Medicinal plant; Bioactivity; Rosa damascene

Abbreviations / Acronyms:
AIDS: Acquired Immunodeficiency Syndrome; **GE:** Geraniol; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **TD:** Thymus Daenensis.

Note:
This study has followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (http://www.prisma-statement.org). PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. PRISMA focuses on the reporting of reviews evaluating randomized trials, but can also be used as a basis for reporting systematic reviews of other types of research, particularly evaluations of interventions.

1. Introduction

Medicinal plants have always been regarded as one of the best therapies for human health problems. Many traditional medicinal plants have been examined for their antitumor potential in cell culture or in animal models (1,

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2). They indicate anticancer effects via inhibiting cancer-activating enzymes, stimulating the production of protective enzymes, encouraging DNA repair, promoting antioxidant action and enhancing body immunity (1). Bioactive molecules as secondary metabolites of plants show defense mechanisms against herbivores, predation, microbial invasion, fungal attack, viral infection and microbial invasion. These molecules can be obtained from essential oils. Natural and bioactive compounds possess properties including disease preventing, health promoting or medicinal properties. There are three major groups of secondary metabolites that include: nitrogen-containing substances, terpene and phenolic (3-7).

The terpenoids represent one of the largest groups of secondary metabolites which are synthesized via the five-carbon building block isoprene (8, 9). The main groups are monoterpenes, sesquiterpenes, diterpenes, triterpenes, steroids and tetraterpenes with 10, 15, 20, 30, 27 and 40 carbon atoms, respectively. Terpenes may have complex structures because of various chemical groups and secondary ring formations. Mono- and sesquiterpenes are often volatile and can be distilled as essential oils, for example, menthol, thymol and thujone. They occur in several families including *Asteraceae, Lamiaceae, Lauraceae, Rutaceae* and *Zingiberaceae*. Terpenes often have antimicrobial and cytotoxic activities against a range of organisms and may be used to treat bacterial and parasitic infections as well as respiratory disorders (10, 11). Citronellol, geraniol (GE), nonadecane and phenylethyl alcohol are the most important compounds in the essential oil of *Rosa Damascene* (12-18). Plant secondary metabolites have a wide range of biological activities, and thus have been used in traditional medicine. Synthetic pharmaceuticals are made from single chemicals whilst phytomedicines commonly wield their favorable effects via the synergistic action of several phytochemical compounds acting at single or multiple target sites linked with a physiological process (19-21). The aim of the present review is to give a useful summary of the published data on the biological properties of GE.

2. Material and Methods

2.1. Research design and search strategy

In this study we chose to search through the range of resources available from digital / electronic libraries in all English-language publications aiming to raise public health awareness (Figure 1). Topics relevant to this review were assessed. The results of this study were investigated based on articles published in Iranian and international journals. In this study, all published articles from 1940 to the end of 2020 were chosen by searching the databases of Embase (n=236), Scopus (n=318), ScienceDirect (n=43), Clarivate Web Of Science™ (n=308) and PubMed (n=163). Articles were searched using English keywords and prefixes such as geraniol OR health OR bioact OR anti OR benef OR treat OR therap OR pharma OR fung OR microb OR propert individually and combined or articles in the reference list.

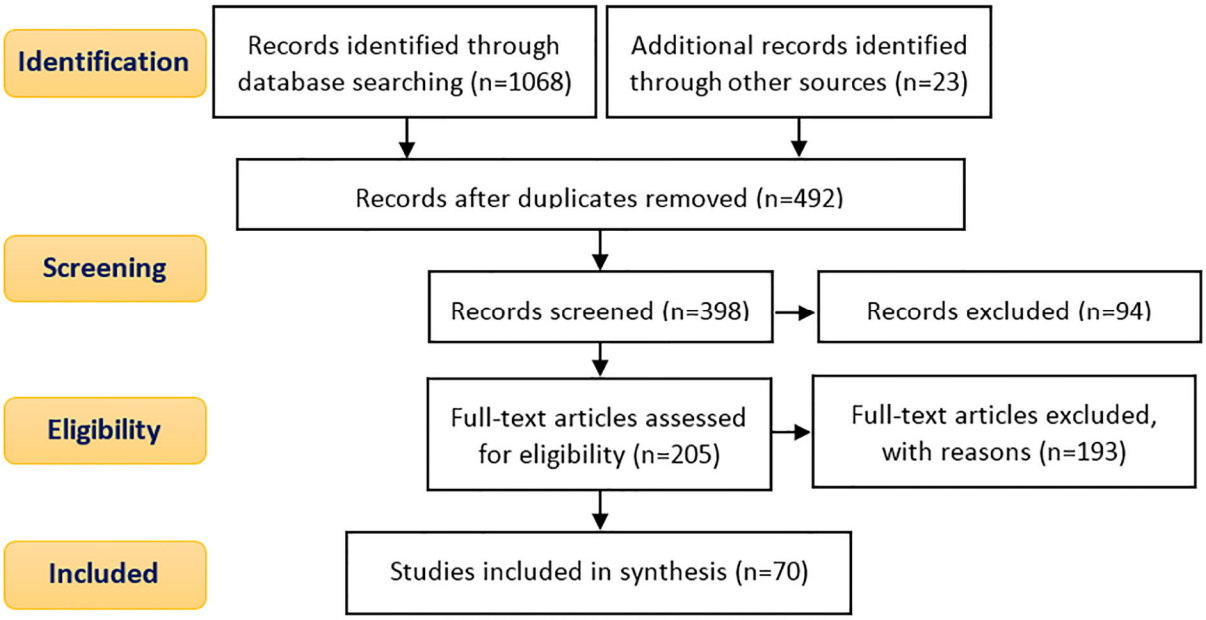

Figure 1. Flowchart of information in different phases of the systematic review

2.2. Inclusion and exclusion criteria

All evidence into a qualitative form based on inclusion criteria such as all experimental and observational research, the time period (between 1976 and 2020), English language, with setting the health aspect of GE with toxicological and pharmacological effects were carried out. Similarly, other criteria were considered as exceptions.

3. Results and Discussion

3.1. Rosa Damascena Mill

The production of favorable odors using flowers and leaves has a long history (Figure 2). Essential oils are the most useful and valuable natural perfume oils extracted from rose plants. Although only approximately 20% of the wild species are in the group of 'fragrant' compounds, over 400 volatile compounds have been found in rose oil (22). In the case of essential oils, there is a strong relation between their content and composition with species and cultivars. Currently, rose oils (attar of roses) and a semisolid extract (rose concrete) are produced using *R. Damascena* (Bulgarian rose oil) and R. Centifolia (Moroccan rose oil) which are commercially the most important species; Turkey, Iran, Bulgaria and Russia are the major regions for the production (23). In Iran, Rosa damascenes Mill, which is known as Damask Rose (22), is named Gole Mohammadi (23). It is one of the main species of the Rosaceae family which is widely used as an ornamental plant and has been named as the king of flowers (24). To date, more than 2000 rose species and over 18000 cultivars have been recognized (25). Rosa damascene Mill (R. damascene) is an aromatic plant with light pink flowers that blossom in spring (26). Iran is one of the main origins of R. damascene (27) and its cultivation and consumption have a long history in this country (3, 28, 29). Until the 16th century, the main producer and exporter of rose oil throughout the world was Iran (30, 31). The compositions of *R. damascena* essential oil growing in Iran and analyzed by GC/MS are indicated in Table 1. It's widely used for the purpose of decoration and perfumery (32). In addition to this property, it is greatly cultivated for its medicinal properties. Recent studies have indicated that anti-HIV, antioxidant and anti-bacterial activity essential oils can be extracted from *R. Damascena* (33-39). The rose oil is recognized as one of the most expensive essential oils in the world due to the low amount of Rosa genus oil and the lack of natural and synthetic substitutes (36-39). This plant has a lot of advantages such as being a cardiotonic agent, and having anti-inflammatory, astringent cooling and soothing effects (40). Recently, aromatic plants rich in essential oils have become of interest in food products due to their antibacterial and antioxidant properties (41). Based on the chromatographic results, citronellol (14.5-47.5%), GE (5.5-18%), heneicosane (7-14%) and nonadecane (10.5-40.5%) were major components of *R. damascena* oil (Kashan, Iran) (23). In a number of studies, citronellol, GE and nerol were found to be three main components of rose oil, which possessed strong antimicrobial activity (42, 43). The essential oils of Rosa damascene are found to be the most suitable precursors for medicinal, and perfumery applications as well as cosmetic preparation (34, 36).

Figure 2. The plant of R. damascene

Table 1. Chemical constituents (%) of the essential oil of *Rose damascena* in Kashan (Barij Essence Pharmaceutical Company)

No.	Compound	RI	RT Rose EO	Concentration (%)	No.	Compound	RI	RT Rose EO	Concentration (%)
1	α-Pinene	933.7	5.92	0.3931	35	α-humulene	1456	19.45	0.3299
2	β-Pinene	978.1	6.98	0.0443	36	Geranyl propanoate	1474	19.9	0.0695
3	β-Myrcene	989.9	7.08	0.1447	37	Germacrene D	1484	20.07	0.5418
4	p-Cymene	1024	8.19	0.0793	38	β-Selinene	1489	20.34	0.2318
5	Limonene	1029	8.39	0.0458	39	pentadecane	1498	20.45	0.0987
6	1,8-Cineole	1032	8.52	0.0532	40	α-Muurolene	1501	20.49	0.2484
7	Linalool	1102	10.22	3.7261	41	δ-Guaiene	1508	20.87	0.6127
8	Nonanal	1104	10.37	0.7168	42	Δ-Cadinene	1526	21.02	0.0454
9	cis-Rose oxide	1112	10.83	0.2615	43	Citronellyl butanoate	1527	21.09	0.078
10	Benzeneethanol	1119	11.18	1.2875	44	Geranyl butanoate	1561	21.65	0.2802
11	trans-Rose oxide	1129	11.55	0.0773	45	E-Nerolidol	1565	21.88	0.1115
12	menthone	1156	11.86	0.2338	46	2-Phenyl ethyl tiglate	1588	22.8	0.4795
13	Isomenthone	1167	12.15	1.0996	47	hexadecane	1597	23.06	0.0471
14	4-Terpineol	1181	12.56	0.4124	48	10-epi-γ-eudesmol	1625	23.69	0.2771
15	α-Terpineol	1196	13.05	0.6509	49	γ -Eudesmol	1636	tr	tr
16	β-Citronellol	1240	14.01	50.6268	50	Cubenol	1647	23.82	0.0114
17	Neral	1246	14.18	0.3335	51	β-Eudesmol	1656	23.88	0.0631
18	Carvone	1251	14.27	0.0731	52	α-Cadinol	1659	23.99	0.1294
19	Geraniol	1263	14.59	11.2085	53	E-Citronellyl tiglate	1666	24.08	0.1582
20	Geranial	1275	14.76	0.54	54	Heptadec-8-ene	1675	24.16	0.0604
21	Citronellyl formate	1278	14.76	2.93	55	Heptadecane	1698	24.42	1.0204
22	Neryl formate	1283	14.89	0.1859	56	Geranyl tiglate	1702	24.49	0.0726
23	E-Anethole	1290	14.99	0.1308	57	2z, 6E-Farnesol	1725	24.89	0.2815
24	Geranyl formate	1303	15.45	0.6207	58	Benzyl Benzoate	1768	26.5	0.1373
25	Methyl geranate	1325	16.05	0.1	59	Octadecane	1797	27.14	0.0936
26	Citronellyl acetate	1354	16.53	0.0749	60	1-Nonadecene	1872	28.06	1.6251
27	Eugenol	1361	16.63	0.3741	61	Nonadecane	1900	28.56	7.4944
28	α-copaene	1378	17.39	0.9716	62	1-Eicosene	1970	29.95	0.0663
29	Geranyl acetate	1384	17.44	0.3463	63	Eicosane	1996	30.39	0.8736
30	β-bourbonene	1387	17.55	0.273	64	Heneicosane	2104	32.24	3.2075
31	Methyleugenol	1407	18.43	1.3833	65	Docosane	2196	33.93	0.0545
32	trans-caryophyllene	1422	18.53	1.0404	66	Tricosane	2296	35.59	0.488
33	α-Guaiene	1440	18.77	0.2303	67	Tetracosane	2400	36.67	tr
34	Citronellyl propionate	1443	18.84	0.2203	68	Pentacosane	2440	37.3	0.0298

3.2. Geraniol

Geraniol (3, 7-dimethylocta-trans-2, 6-dien-1-ol) is a compound that is extracted from the flowers of roses and many other plants (44, 45). Geraniol is a natural component of the plant's essential oils which has a rose-like odor and its taste is generally used as a flavoring in the food industry (44) (Figure 3). The U.S. Food and Drug Administration (FDA) approved it as a generally safe component (46). Geraniol, as a clear to pale-yellow oil, is poorly soluble in aqueous solutions whereas has a high solubility in common organic solvents (47). Geraniol presents several remarkable biochemical and pharmacological properties; it is an important plant-based insect repellent (48), it has antimicrobial, antioxidant, anti-inflammatory (49), and strong antibacterial activity (50), and is also an antifungal agent (51) (Figure 4). It shows anti-inflammatory effects on monocytes cell line (52). Geraniol exhibits in vitro and in vivo anti-tumor effects on murine leukemia, hematoma and melanoma cells (53, 54). Geraniol is a primary acyclic, unsaturated terpene alcohol with the chemical formula $C_{10}H_{18}O_4$. It has a distinctive rose-like odor and the taste (at 10 ppm) is qualified as sweet floral rose-like, citrus with fruity and waxy c (49). Geraniol is found in oily tissues of several plants as well as frequently co-exists with its oxidation product like geranial and nerol (47). It is naturally found in many oils like Palmarosa, geranium or rose oils (55). It is also a lead molecule in the development of anticancer drugs (46, 56, 57). Researchers have proven that GE is a useful plant for repelling insects (48). Also, several studies have specified the antimicrobial activity of this compound (51). In in vitro and in vivo studies, GE has been shown to inhibit the growth of murine leukemia, hepatoma and melanoma cells (58, 59).

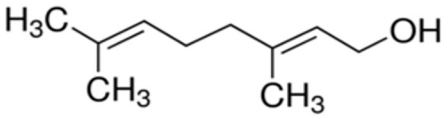

Figure 3. Chemical formula of geraniol

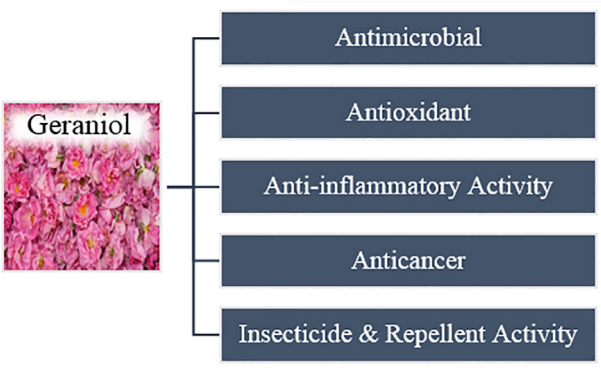

Figure 4. Health benefits of geraniol

3.3. Functional properties of geraniol

3.3.1. Antimicrobial activity

Essential oils show a strong inhibitory effect on many bacteria and fungi. When the essential oils are solved in the phospholipids bilayer of the cell membranes, its antimicrobial effect occurs (60). It was proved that some monoterpene alcohols such as citronellol, geraniol, Linalool and nerol, show more effective antibacterial properties than antifungal properties (61, 62). Gaseous GE presents an antibacterial effect on respiratory tract pathogens, such as *H. Influenzae* and *S. Aureus*. Friedman, Henika (63) compared essential oils (n=96) and oil compounds (n=23) in terms of bactericidal activity levels against *C. Jejuni*, *E. coli, L. monocytogenes* and *S. enterica* from food and clinical sources. Geraniol showed higher activity against *E. coli, L. Monocyto*genes and *S. enterica* with a bactericidal activity value (BA50) of 0.15, 0.28 and 0.15, respectively. Among 60 essential oils tested, GE was able to prevent human and animal pathogens, *S. typhimurium* and *E. coli* (64). Citronellol, GE and nerol presented minimum inhibitory concentrations (MICs) from 64 to 128 µg ml^{-1} against *Mycobacterium tuberculosis* (65). The GE obtained from M/s S H Kelkar, Mumbai was found to show stronger bacterial sensitivity to *E. faecalis, M. smegmatis, P. aeruginosa, S. aureus and S. epidermidis* over the sample obtained from another source. The GE exhibited 312.5 µg mL^{-1} MIC against *E. coli, M. smegmatis, P. aeruginosa, S. typhi* and *Y. enterocolitica*. However, 100 µg mL^{-1} strong activity from GE was found against *S. mutans* (66). Geraniol in an essential oil extracted from Palmarosa leads to the antifungal action against *S. cerevisiae* (67). Geraniol showed a strong antifungal effect on *C.*

albicans. Palmarosa exhibits inhibitory activity against Cryptococcus neoformans, a fungus causing infection during the last stages of AIDS (68). Geraniol displayed 312.5 µg mL^{-1} MIC against *Aspergillus flavus* whereas MIC of 625 µg mL^{-1} was obtained against *Trichophyton rubrum* and *Microsporum gypseum* (66). It has shown the main antifungal activities against *Colletotrichum camelliae* (MIC value 440 µg mL^{-1}) (69). Geraniol (25 µg mL^{-1}), in combination with vaginal washing, mainly inhibited the growth of viable *C. albicans* cells and improved vaginal inflammation (70).

3.3.2. *Antioxidant activity*

Free radicals cause molecular alteration related to Alzheimer's disease, aging, asthma, arteriosclerosis, cancer, and diabetes by oxidation of biomolecules (71). Experimental studies described several pharmacological activities of GE including anticancer and antioxidant activities (72). Mahmoud A. Saleh et al. evaluated the antioxidant activity of various essential oils and showed that the essential oils of the Rosaceae family were among the most effective compounds (73). The radical scavenging activity of *P. graveolens* essential oils was investigated using the 1,1-diphenyl-2-pycrylhydrazyl (DPPH) method. The antioxidant activity values were obtained between 63.70 mg mL^{-1} for leaves to 64.88 mg mL^{-1} for stems (74). Recent studies showed that GE oil had antiradical activity (IC50 = 14.49 mg mL^{-1}) mainly stronger than acetone extract of the plant (IC50 = 66.45 mg mL-1) (75). In a study on evaluating the antioxidant activity of *Thymus daenensis* (TD) containing 66.8% GE, 13.9% geranyl acetate, and 9.6% β-caryophyllene, DPPH radical scavenging represented that TD essential oil extract had higher IC50 values than the antioxidant standards. Moreover, TD extract exhibited lower IC50 value (194.24 ± 0.021 µg mL^{-1}) than TD essential oil (76). In another study, the antioxidant activity of GE, geranyl acetate, gingerol and eugenol were evaluated. Lower IC50 value inferred higher antioxidant activity. Among these essential oils, GE, geranyl acetate, gingerol and eugenol exhibited 24.6, 4.2, 68.4 and 0.9 µg mL^{-1} IC50 values, respectively (77). The essential oils extracted from old leaves and flowers demonstrated the highest scavenging activity, which may be attributed to the presence of GE, nerol and some other terpenes in the Neroli oil (78, 79). The radical scavenging activity of 34 kinds of citrus essential oils and their volatile components was investigated by researchers (80). They used the DPPH method and compared the activity of essential oils with trolox as a standard antioxidant. Geraniol exhibited significant scavenging activity against the DPPH radical (87.7%, 235.9 mg of trolox equiv ml^{-1}). Antioxidant and anticancer effects of geranium oil are related to citronellol and trans-geraniol, the main components of it. Geraniol has a significant inhibitory potential to the growth of tumor cells of pancreas, as well (75). Antioxidant effect of GE in different in vitro models indicates the potential benefit of GE against oxidative stress (OS), a progressive pathological feature of neurodegenerative disorders (81).

3.3.3. *Anticancer activity*

Geraniol exerts protective effects and chemotherapeutic activity toward many human cancers such as pancreatic cancer (58). Geraniol exhibits a new class of chemopreventive cancer agents as it has inhibitory activity on CaCo2 colon cancer cells (57). Geraniol presents in vitro and in vivo antitumor activity against several cell lines. In fact, it changes several lipid metabolic pathways of HepG2 cells such as mevalonate pathway and the phosphatidylcholine biosynthesis, which leads to inhibited cell growth, and cell cycle impedance that is occurring at the G0/G1 interphase and enhanced apoptosis (82). Geraniol has significant (60-90%) inhibition of the anchorage-independent growth of human MIAPACa2 pancreatic tumor cells (58). Crowel reported that dietary GE obstructed hepatic HMG CoA reductase activity and decreased the level of serum cholesterol in experimental animals (83). The interaction of GE with 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase is reported (84). It has been found that GE can prevent proliferation, cell cycle progression and cyclin-dependent Kinase 2 activity in MCF-7 breast cancer cells with no effect on the activity of HMG-CoA reductase (85). A study revealed that GE inhibits prostate cancer growth and also enhances the sensitivity of the affected cells to chemotherapeutic agents (86). Manoharan and Selvan (87) found that oral administration of GE to 7,12 dimethylbenz(a) anthracene (DMBA) treated mice, prevented the formation of tumor in 83% of animals. Furthermore, GE significantly decreased the histological abnormalities in the skin tissues of DMBA daubed mice. They also presented that GE may have inhibited unnatural cell accumulation in skin tissues during DMBA induced skin carcinogenesis. They reported that oral administration of GE mainly enhanced the activities of phase II enzymes and the level of glutathione in DMBA daubed mice. These results present that GE provoke the activities of phase II detoxification cascade to ward off the active metabolite of DMBA, the dihydrodiol epoxide. The antitumor activity of GE is thus partially in relationship with an induction of phase II detoxification enzymes and their antioxidant enzymes. They also presented chemo-preventive ability of GE in DMBA-induced skin carcinogenesis. It can be concluded that this ability of GE could be attributed to properties including anti-lipid peroxidative, antioxidant and modulatory effect on carcinogen detoxification process during DMBA-induced skin carcinogenesis.

3.3.4. *Insecticide and repellent activity*

Essential oils of a large number of plants have the ability to be repellent against various Hematophagous arthropods (88, 89). They also presented repellent, and/or antifeedant effects and insecticidal action against insects (48). Geraniol and eugenol are effective attractants and are able to trap Japanese beetles, Popillia japonica Newman (90). It was shown that mixing doses of citronella, lemon (citrus lemon), rose (*Rosa damascene*), lavender or basil essential oils with distilled water is very efficient in preventing indoor insect pests (91). Hierro, Valero (92) have investigated the activity of some monoterpenoid compounds against Anisakis simplex. The results showed the activity of GE, citronellol, citral, carvacrol and cuminaldehyde at 125.5 µg mL^{-1} concentration. Geraniol and a number of compounds were found as fumigants against Musca domestica and *T. castaneum*. Geraniol, carveol, carvacrol, linalool, menthol, terpineol, thymol, verbenol and some other compounds are ovicidal against *M.domestica* eggs (93). The acaricidal activities of GE from *Pelargonium graveolens* oil on *Tyrophagus putrescentiae*, and the storage food mite, and comparing its activity with benzyl benzoate has been surveyed. The results showed that GE was more effective than benzyl benzoate with the 50% lethal dose value being 1.95 µg cm3 and 1.27 µg cm3, respectively (94). Mosquito bites lead to allergic responses and transfer several diseases such as malaria, yellow fever and dengue (95, 96). It has been proved that GE is an effective mosquito repellent (97). Geraniol-based products are available in several countries as natural repellents. It was found that GE candles were more effective than linalool and citronella candles in protecting a person from bites of mosquitoes and sand flies (98). A study comparing three botanical natural repellents proved that the longest protection time of a person from bites of mosquitoes was attained when lemongrass extract was combined with 25% GE oil (99).

3.3.5. *Anti-inflammatory activity*

Inflammation is a normal protective response provoked by tissue injury or infections, and functions to conflict invaders in the body (100). There is some evidence that essential oils have anti-inflammatory activity (101). For instance, citral, GE, citronellol and carvone can prevent the formation of pro-inflammatory cytokines such as TNF-α (102). It is proven that GE and some essential oils inhibit the formation of leukotriene, as a mediator of inflammation. Hence, they are beneficial in the treatment of various inflammatory diseases, including asthma, chronic bronchitis and allergic rhinitis among others (103). The studies that performed the anti-allergic effects (allergic rhinitis or pollinosis) of flavored and non-flavored chewing gums displayed that gums fortified with peppermint oils such as geraniol, 1-menthol, citronellol and 1, 8 –cineole were more efficient in decreasing rhinitis symptoms in comparison with non-flavored gums and normal peppermint-flavored gums (104, 105).

4. Conclusions

Rosa damascena, the most important member of Rosacea species, is chiefly familiar for its perfuming. Rose water and essential oil are major products of this plant. This plant has several components such as flavonoids, terpenes, anthocyanin and glycosides with useful effects on human health. One of the major compounds of *Rosa damascene Mill* is geraniol. It is the most abundant monoterpene presented in many plants. It is one of the major compounds of *Rosa damascene Mill* and is widely used as a fragrance and flavor material in the food industry in order to treat infectious diseases or acting as a preservative. Geraniol presents several remarkable properties such as anti-cancer, antioxidant, antimicrobial, insect repellent and anti-inflammatory activities. Its antimicrobial effect on a large number of bacteria and fungi has been proven. Geraniol as a lipid-soluble (non-polar) component exhibited significant scavenging activity against the DPPH radical and displayed anticancer activity in both of the in vitro and in vivo states in some of the human cancer models. Geraniol is also recognized as a natural pest control agent with low toxicity, because of its insecticidal and repellent properties.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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