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Review

A systematic review of the efficacy and safety of *Rosa damascena* Mill. with an overview on its phytopharmacological properties

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ABSTRACT

Rosa damascena Mill. is one of the most famous ornamental plants cultivated all over the world mostly for perfumery industries. Traditionally it has been used as an astringent, analgesic, cardiac and intestinal tonic.The paucity ofauthoritative monographs urged usto summarize its clinical effectiveness and safety with acomprehensive review of the literature.

"PUBMED", "SCOPUS", "WEBOF SCIENCE" were searched up to April 30, 2017 with search terms:("*Rosa damascena*" OR "Damask Rose"). All human studies with any mono-preparation were included. In vitro and animal studies from "PUBMED"were also reviewed and outlined.

Of "1000" identified publications, twelveeligibleclinical trials were retrieved. Antimicrobial, anti-inflammatory, antioxidant, anticancer, protective neuronal, cardiac, gastrointestinal and hepatic effectsin 30 *in vitro* and 21 animal studies were also shown. there are promising evidences for the effectiveness and safety of *Rosa damascena* Mill in pain relief, but confirmatory studies withstandardized products is suggested.

1. Introduction

In the early years of the twenty first century, as the prevalence and morbidity of chronic diseases increased, it became more important to explore new treatment methods.[1] Herbal medicine is one of the most popular and ancient ways of treating ailments and has come under scientific investigations.[2,3] One important question is whether herbalism is effective and safe, therefore systematically conducted reviews answer relevant questions. *Rosa damascena* Mill. *(R.damascena),* known as Damask rose, a perennial bushy shrub, is the most famous ornamental plant of the Rosaceae family worldwide, in terms of perfumery and food industries.[4] Although the essential oil of Damask rose is thoroughly documented in herbal references,[5,6] hardly could it be detected in European authoritative monographs.[7,8] This may be due to its greater popularity in the eastern part of the world, where it has long been used traditionally as a herbal medicine.[9] Historically, Damask rose originated from the middle east and was then brought to Europe.[10,11] Oil extraction by crude distillation of roses probably began in Persia in the late 7th century AD, and was later developed in the provinces of the Ottoman Empire.[12] For a very long time, Damask rose has been very important in traditional polyherbal formulations.[13] More than one thousand years ago Avicenna (980–1037 AD)[14] described the various medical benefits of Damask rose such as its gastrointestinal and cardiac tonic effects, cosmetic properties in eliminating the unpleasant odor of sweat, repair of skin and mucosal lesions and he also mentioned its antinociceptive and anti-inflammatory virtues.[15] Later, Aghili Shirazi (1670-1747 AD)[16] in his famous book "Storehouse of Medicaments" discussed its medicinal effects as a brain tonic and pain killer in a variety of diseases.[17] Today, *R.damascena* is largely cultivated all over the world mostly in Turkey and Bulgaria as a result of its fragrances, flavourings and medicinal properties.[4,18] It is also massively harvested from gardens in Iran, India, China, northern African countries and Europe.[18] Different products such as rose oil, rose water, dried petals and hips of the plant are commercially derived and consumed. Alcoholic, aqueous, hydro-alcoholic or other kinds of extracts from different parts of the plant mainly the flowers are also academically prepared for research.[11]

Pharmacological studies have shown the various health effects of *R.damascena* flowers which can mainly be attributed to its large amount of polyphenolic components. A wide range of phytochemicals including

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flavonoids, glycosides, terpenes, and anthocyanins have been isolated from different parts of the plant.[4,19] Vitamins C, A, B1, B2, B3, and K, citric acid, malic acid, pectin, tannins and carotenoids have also been reported.[20] Major active phenolic compounds are kaempferol, cyanidin 3, 5, D-glycoside, quercetin, and gallic acid.[19] β Citronellol, nonadecane, geraniol and henicosane are the main chemical constituents of its volatile oil.[21] Although different concentrations of rose oil components have been reported from different parts of the world,[10] few studies have compared the constituents of different extract types.[22–30] The total phenolic contents of the rose essential and absolute oil are higher than the hydrosol (water aroma). While phenyl ethyl alcohol is the major component of rose absolute[31] and rose water volatiles[29,30] citrenellol and geraniol constitute more than 55% of rose essential oil and hydrosol. The presence of much higher levels of some components in the hydrosol compared to the rose oil was remarkable such as geraniol: (30.74% versus 22.19%) and nerol:(16.12% versus 10.26).[31]

Apart from its pharmacological effects such as "hypnosis, analgesia, neuroprotection; anti-convulsion, cardioprotection, bronchodilatory, antimicrobial and digestive beneficial effects, anti-inflammation, antioxidation and anti-diabetes", few studies have surveyed its clinical efficacy and safety.[4,32–35] The aim of this review was to summarize the current evidence for the clinical efficacy and safety of *Rosa Damascena* Mill. with an overview on its phytopharmacological properties.

2. Methods

2.1. Search strategy

Systematic search was electronically conducted in following databases: PUBMED, SCOPUS and WEB OF SCIENCE, all from the inception date till the end of April 2017 to identify all published investigations on "*Rosa Damascena* Mill.". The database named "The plant list"[36] was previously searched and the synonyms and accepted names of the plant were checked. The selected search terms were ("*Rosa damascena*" OR "Damask Rose") without limiting search elements. In PUBMED database the search field was "Title/Abstract", in SCOPUS database was "Title/Abstracts/Keywords" and in WEB OF SCIENCE was "Topic". Furthermore handsearching the bibliographies of retrieved results and reviews to obtain additional relevant studies was performed.

2.2. Study selection

Two reviewers independently reviewed all the results and extracted data while meeting inclusion and exclusion criteria. All human studies with intervention of any mono-preparation of "*Rosa damascena*" OR "Damask Rose" were included. In vitro and animal studies investigating any pharmacologic effect of the plant extracts or its certain isolated constituents along with toxicologic studies were also selected from PUBMED database and included in relevant tables. Review articles, letters to the editor, book sections, unpublished data such as theses and publications without available English abstracts were excluded.

2.3. Data extraction

All the abstracts and related full texts of selected articles were reviewed and following items were extracted and summarized in relevant tables. In (Table 1) the following items of *in vitro* studies were extracted: 1) first author's name and the year of publication 2) the type of extracts 3) the recorded pharmacologic activities 4) the components if detected in the study 5) the related medical or biological effect 6) any suggested mechanism based on results of the study. In (Table 2) experimental studies in animals were extracted as follows: 1) first author's name and the year of publication 2) the target of the experiment 3) the type of extracts 4) doses/route of administration/study duration 5) main exhibited outcomes 6) adverse effects and after a slash(/) summarized biologic effect. For human studies in (Table 3) following items were included: 1) first author's name and the year of publication 2) the type of study and after a slash (/) the Jadad score identified for assessing the quality of the report based upon the Jadad scaling method.[37] 3) description of participants and their number and ages 4) the product or the extract type 5) doses/route of administration/duration of the intervention 6) study groups 7) major outcomes of intervention 8) any reported adverse effects and after a slash (/) any scientific definition or precious comment summarizing the study. Non-available data after email contacts to authors and not receiving responses were noted in tables as: "Full text not found".

3. Results

The preliminary search of databases have identified "1000" related publications. Twelve randomized controlled trials (RCTs) for any indication were reviewed as human trials and presented in Table 3. The flow-chart is outlined in Fig. 1. Any other type of clinical trials was not reported. Furthermore, "30" *in vitro* experiments and "21" animal studies were reviewed and outlined in Tables 1 and 2, respectively.

3.1. In vitro studies

3.1.1. Antimicrobial activity

Multiple studies have demonstrated the antibacterial and disinfectant activity of *R. damascena Mill.* and indicated the role of large phenolic contents such as flavonoids, terpenoids and phenyl ethyl alcohol.[28,38–41] Zu et al. investigated the activity of several essential oils against *Propionibacterium acnes*.[42] and revealed the potent anti-acnea effect of *R. damascena* Mill. Shokouhinejad et al. noted its comparable effect with chlorhexidine against endodontic pathogens.[43] Mahmood et al. tested the isolated constituents of its methanolic extract against HIV virus and detected different antivirus mechanisms indicating the synergistic effect of components together in the whole plant.[44] It is notable that no antimicrobial effect of its hydrosol has been reported.[28] and anti-fungal activity was only detected by its aqueous extract against *Candida albicans*.[38]

3.1.2. Anti-inflammatory activity

In Zaidi's study, 70% hydro-alcoholic extract of *R. damascena* Mill. with 100 μg/ml concentration exhibited potent inhibition on IL-8 secretion, in *Helicobacter pylori* infection.[45] Slavov et al. in (2013) introduced a water-soluble polysaccharide named (RP-1) from distilled rose petals of *R. damascena*. They noted its potent immunomodulatory effect on mice intestinal Peyer's patch cells and IL-6 producing activity from macrophages.[46] Three years later, Wedler et al. detected a significant decrease in gene expression and cellular protein secretion of pro-inflammatory biomarkers by polyphenolic fractions of rose oil distillation waste water.[47]

3.1.3. Antioxidant activity

Various studies detected the anti-oxidative effect of *R. damascena* Mill. by 1,1-diphenyl-2-picryl hydrazyl (DPPH) assay.[23,26,48] A variety of polyphenolic compounds, mostly the glycosides of kaempferol and quercetin were derived from the methanolic extract and suggested as active antioxidative components and DNA protective agents.[23,26] However, after comparing the antioxidant properties of 10 medicinal plants, Moein et al. concluded and noted the DPPH radical scavenging effect of the ethanolic extract, as a consequence of existing non-phenolic compounds.[48] Sedighi et al. also demonstrated the antioxidant activity of a 70% hydro-alcoholic extract of Damask rose by the ferric thiocyanate method, 78% equivalent to rutin (a standard flavonoid compound).[22]

3.1.4. Anticancer effects

Many studies presented the prominent cytotoxic effects of *R. damascena* Mill. methanolic extract.[49] and rose oils[42,50–52] against cancer

Table 1
In vitro studies on *Rosa damascena* Mill.

First author/year	extract	Pharmacological activities	Detected components	Medical effect	Suggested or detected mechanism
Wedler et al. (2016)[47]	A polyphenol enriched fraction (RF20-SP207) from rose oil distillation waste water	Sig. decrease in gene expression and cellular protein secretion of IL-1β, IL-6, IL-8, RANTES and MCP-1.	A phenolic fraction (RF20-SP207) and its four subfractions	Potential anti-inflammatory activity	Markedly modified inflammatory target gene expression
Artun et al. (2016)[49]	Methanolic extract	Potential anticancer activity (IC50: 265 μg/ml on HeLa cells and > 1000 mg/ml on Vero cells). High toxicity against cancer cells (SI values > 3.8)	Not detected	Promising anticancer activity	Not mentioned
Solimine et al. (2016)[59]	A polyphenol enriched fraction (RF20-SP207) from rose oil distillation waste water	Strong anti-tyrosinase activity (IC50: 0.41 μg/ml) and both competitive and uncompetitive activity 10 times more potent than that of the positive control kojic acid	Quercetin, kaempferol and ellagic acid	Potent anti-hyperpigmentation in cosmetic products	anti-tyrosinase activity much more potent than kojic acid
Tofighi et al. (2015)[40]	A crude extract: methanol macerated petals then concentrated in vacuum	Antibacterial activities against *Bacillus cereus, Staphylococcus epidermidis, S. aureus and Pseudomonas aeruginosa* with MICs 70, 140, 560 and 140 μg/ml, respectively. no antifungal activities was shown.	Not detected	Antibacterial and disinfectant activity	Flavonoid antibacterial properties were suggested
Mizuno et al. (2015)[53]	Essential oil	H2O2-induced neuronal death reduction and protective effects against aluminum-induced neurotoxicity	Not detected	Neuroprotective effect on immortalized hypothalamic neurons	Antioxidant properties were suggested for increase of viability against H2O2
Dolati et al. (2013)[57]	Aqueous fraction	Compared to controls without extract sig. dose dependent increase in the basal guinea pig ileum contraction (0.66, 0.83, and 1.3 mg/ml). Maximal dose contraction induced 23.4% of maximal Ach response.	Not detected	mild laxative agent in ginea pig ileum.	Sig. contraction decrease with 0.001 μg/ml of atropine suggested the mediation of muscarinic receptors
Sedighi et al. (2014)[22]	Hydro-alcoholic extract	Cumulative doses (100, 500, and 1000 mg/L) decreased ileum contractions induced by KCl (60 mM) dose-dependently. The antioxidant activity was 78% equivalent to rutin.	Total flavonoids: 48.5 mg/100 g and phenolic compounds: 109.1 mg/100 g (equivalent to gallic acid).	Decreased the isolated ileum movements of the rat.	Sig. decrease of the extract inhibitory effect by propranolol, naloxone and calcium, suggested the mediation of β-adrenergic and opioid receptors and voltage-dependent calcium channels
Sadraei et al. (2013)[92]	Essential oil, geraniol and citronellol derived components	The essential oil dose dependently(2.5–160 μg/ml) inhibited the response to KCl (IC50 = 67 ± 8.4 μg/ml) and to electrical field stimulation (IC50 = 47 ± 10.6 μg/ml), Geraniol (IC50 = 1.7 ± 0.15 μg/ml for KCl) and citronellol (IC50 = 2.9 ± 0.3 μg/ml for KCl)	Of 34 isolated compounds, main constituents: β-citronellol (23%), nonadecane (16%), geraniol (16%) heneicosane (5%)	Decreased the isolated ileum movements of the rat. geraniol and citronellol were 40 and 20 times more potent than the essential oil respectively.	Geraniol and citronellol had a major role in inhibitory effect of ileum contraction.
Sadraei et al. (2013)[55]	Hydro-alcoholic extract	1–8 mg/ml dose dependently inhibited ileum contraction induced by KCl (IC50 = 3.3 ± 0.9 mg/ml), ACh (IC50 = 1.4 ± 0.1 mg/ml) and electrical field stimulation (IC50 = 1.5 ± 0.3 mg/ml)	Not detected	stimulatory effect on rat ileum smooth muscle at micrograms dosage but inhibitory effect at higher doses (milligrams)	Different effects with different doses may be likely due to presence of different components in the extract
Jazayeri et al. (2014)[54]	Aqueous-methanolic extract	Inhibition of acetylcholinesterase activity (IC50 = 93.1 μg/ml)	Not detected	Effective in memory enhancement and Alzheimer desease	Not mentioned
Hagag et al. (2014)[50]	Concrete and absolute rose oils	absolute rose oil had sig. antimutagenic activity at a dose of 10 μg/ml. Both rose concrete and absolute oils showed anticancer activity against HepG2 and MCF7 cell within the National Cancer Institute criteria (IC50 < 20 μg/ml), Both extracts were cytotoxically and genotoxically safe at a dose of 10 μg/ml on normal human blood lymphocytes.	major aroma compounds in concrete oil: phenyl ethanol (37.83%), b-citronellol (8.2%), geraniol (4.04%), eugenol(1.48%) in absolute oil: phenyl ethanol(33.31%) b-citronellol (12.45%), geraniol (6.28%), eugenol (2.03%)	concrete and absolute rose oils are safe on normal human blood lymphocytes along with anticancer properties	High level of phenyl ethanol may be one of the responsible constituents along with previously identified geraniol and eugenol for the anticancer properties
Boskabady et al. (2013)[58]	Aqueous-ethanolic extract	sig. dose dependent (0.1, 0.2, 0.4 and 1.0 mg%) increase in both heart rate and contractility but more in heart rate and reverse of propranolol effect.	Not detected	A potent inotropic and chronotropic effect on isolated guinea pig heart	Possible stimulatory effect on beta-adrenoceptors along with several mechanisms of action
Slavov et al. (2013)[46]	A pectic polysaccharide (RP-1) from waste rose petals	intestinal immune system activity modulation through Peyer's patch cells and macrophages IL-6 production	Carbohydrate fractions mainly of galacturonic acid, arabinose, galactose	Immunomodulating effect in mice intestine	may be due to active carbohydrate structures such as the arabino-3,6-galactan present in the waste of rose petals
Thuncharoen et al. (2013)[51]	Plant extract (S & J international enterprises public company limited)	Dose dependently inhibited skin cancer cells (IC50:3.22 μg/μL) and induced typical apoptotic cell morphological changes at 10 μg/μL	Not detected	Effective anti-proliferation and induction of apoptosis cell death in skin cancer cells.	Not mentioned

(continued on next page)

Table 1 *(continued)*

First author/year	extract	Pharmacological activities	Detected components	Medical effect	Suggested or detected mechanism
Moein et al. (2012)[48]	Ethanolic extract	DPPH free radical scavenging with (IC50: 287.9 ± 5.675 μg/ml). IC50 for gallic acid is 25.32 ± 5.593 μg/ml	Total phenolic Content in mg/g, Mean ± SD was: (2.63 ± 0.16)	Antioxidant activity	Non-phenolic compounds were suggested to be involved in DPPH radical scavenging
Rezaie-Tavirani et al. (2013)[52]	Essential oil	The water soluble phase increased cell growth of both human colon cancer cell line SW742 and human fibroblast cells in high volumes(10 μl) but in lower volumes only fibroblasts were stimulted. the non-soluble phase (inner controls) inhibited both cell types proliferation	Not detected	Stimulating and inhibiting cell growth by different parts of the oil along with anti cancer properties	The water soluble part can act as a growth factor and the evaporated part as an anticancer
Zaidi et al. (2012)[45]	70% aqueous-ethanol extract	Strong inhibitory activity at 100 μg/ml on IL-8 secretion in *Helicobacter pylori*-infected cells.	Not detected	Anti-inflammatory effects in *Helicobacter pylori* associated gastric disorders	As *Helicobacter pylori* viability or toxicity did not alter, anti-inflammation may be through some other mechanisms.
Kalim et al. (2010)[23]	Methanolic (50%) extract	IC_{50} values for scavenging DPPH(·), ABTS(·+), NO, (·)OH, $O_2(\cdot^-)$ and $ONOO(^-)$: (IC50: 10.36 ± 0.02; 3.57 ± 0.11; 273.18 ± 3.52; 23.01 ± 0.03; 42.10; 637.57 ± 52.93 μg/ml respectively. Sig. oxidative DNA damage preventive activity. No cytotoxic activity against U937 cells.	Phenolic content: 142.23 ± 0.09 mg GAE/g extract, flavonoid content: 151.32 ± 0.51 mg QEE/g extract, AA content: 0.82 ± 0.092 mg AA/g extract	Potent antioxidant activity	May be due to the diverse phytochemical contents such as flavonoids and phenolic compounds
Talib and Mahasneh (2010)[38]	Ethanol, methanol, aqueous, butanol, and *n*-hexane extracts	Butanol extract: high inhibition (100%) against *Salmonella typhimurium* and *Bacillus cereus* (MIC: 62.5 and 250 microg/mL). Aqueous extract: active against *Candida albicans* (MIC of 125 μg/ml) Methicillin-resistant *Staphylococcus aureus* was inhibited by both butanol and aqueous extracts (MIC:500 μg/ml) Ethanol extract: had low toxicity against Vero cell line (IC50: 454.11 μg/ml)	Flavonoids and terpenoids	Potential activity against Gram positive and negative bacteria and fungi	Not mentioned
Shokouhinejad et al. (2010)[43]	Extract (full text not found)	MICs of 2% rose extract and 2% chlorhexidine on selected endodontic pathogens, except F. nucleatum, were lower than that of 5.25% NaOCl.	Not detected	Potent anti bacterial activity against endodontic pathogens	Full text not found
Kwon et al. (2010)[24]	Flavonoids from the buds	High inhibitory activity against HMG-CoA reductase (IC(50) from 47.1 to 80.6 mM) of compounds derived from Ethyl acetate solvent except cyanidin-3-*O*-beta-glucoside that significantly suppressed ACE-1 activity (IC(50): 138.8 mM)	A new flavonoid glycoside: roxyloside other fractions: isoquercitrin, afzelin, cyanidin-3-*O*-beta-glucoside, and quercetin gentiobioside	Cardioprotective effect	Bioactive phenolics may in part act as inhibitors
Awale et al. (2011)[25]	Chloroform extract	Sig. neurite outgrowth activity and suppression of the Amyloidβ fraction(25–35)-induced atrophy and cell death.	A very long polyunsaturated fatty acid: C(37)H (64)O(2)	Beneficial effect against dementia was shown	The isolated compound may act as a nerve growth factor (NGF)
Zu et al. (2010)[42]	Essential oil	Moderate antibacterial activity towards *Propionibacterium acnes*, with inhibition diameters of 16.5 ± 0.7 mm and MIC of 0.016% (v/v), strong bactericidal activity at 0.031% (v/v), after 5 min strong cytotoxic effects against cancer cell lines were shown	Not detected	Moderate anti-bacterial activities towards *Propionibacterium acnes* and strong anticancer activities	May be due to complex constituent mixtures, including monoterpenes and sesquiterpenes
Ulusoy et al. (2009)[31]	Absolute oil, essential oil and hydrosol	strong antibacterial activity of absolute and essential oil against *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, Chromobacterium violaceum and Erwinia carotovora strains.* Hydrosole showed no antimicrobial effect.	Absolute oil: higher levels of phenylethyl alcohol(78.38%) and β- caroten, α and γ-tocopherol essential oil and hydrosol: citrenellol and geraniol (> 55%)	Antibacterial effect of absolute and essential oil	Phenolic compounds may contribute to antibacterial effects but stronger effects of rose absolute can be due to its high phenylethyl alcohol content
Kumar et al. (2009)[26]	Methanolic extract	scavenging DPPH(·), (IC50: 21.4 μg/ml) lower than that of other more potent rose species	Phenolic constituents: hydrolysable tannins, flavonols and their glycosides	Antioxidant effect	May be attributed to polyphenolic compounds mainly quercetin, kaempferol and their glycosides
Tabrizi et al. (2003)[27]	Water: ethanol (50: 50), ethyl acetate: ethanol (80: 20) and ether extracts of flowers	All extracts at 20 mg% effectively absorbed UV radiation in 200–400 nanometre range. Cream of 5% ether extract showed the most desirable appearance and stability	Flavonoids as the major components of all extracts, higher in ether extract	Antisolar property	The ether extract UV absorption property is mainly because of higher amounts of flavonoid compounds
Boskabady et al.	Ethanol extract and	Relaxing trachea in all doses of the ethanol	Not detected	Relaxant effects on guinea pig	May be due to β-

(continued on next page)

Table 1 *(continued)*

First author/year	extract	Pharmacological activities	Detected components	Medical effect	Suggested or detected mechanism
(2006)[60]	essential oil	extract (0.25, 0.5, 0.75, and 1.0g%) and essential oils (0.25, 0.5, 0.75, and 1.0 vol.%) comparable with theophylline. ethanolic extract was less effective		precontracted tracheal chains	adrenoceptors stimulatory effect and/or inhibitory effect on histamine H1 receptors. The inhibiton of calcium channels was also proposed
Basim and Basim (2003)[41]	Essential oil	Potential antibacterial activity against three strains of *Xanthomonas axonopodis* spp. *Vesicatoria*	Not detected	Effective in the management diseases caused by bacteriae in tomato and pepper plants	Not mentioned
Andoğan et al. (2002)[39]	Essential oil	Antimicrobial activity against *Staphylococcus aureus* (8 mm: zone of inhibition) and not to *Escherichia coli*. citronellol, geraniol and nerol were more potent than the extract	Citronellol(%10.3), geraniol(%2.8),nerol (%1.3),linalool (%0.6), Redistillated oil:Citronellol (%46.7), geraniol (%23.3), nerol (%11.9), linalool (%0.8)	Antibacterial activity	More potent isolated citronellol, geraniol and nerol compounds with antibacterial activity suggest their main role
Mahmood et al. (1996)[44]	9 compounds isolated from the methanol extract	tetrahydroxyflavanone (kaempferol, 1,): effective reduction of the maturation of HIV virus progeny by selective inhibition of protease. pentahydroxyflavone (quercetin, 2) and two 3-substituted derivatives of kaempferol: binding of gp120 to CD4 prevention 2-Phenylethanol-*O*-(6-*O*-galloyl)-beta-D-glucopyranoside 8: virus neutralization by interaction with gp120	Not detected	Moderate anti-HIV effects	Different isolated compounds acted synergistically against different stages of virus replication such as inhibiting the viral protease and prevention of CD4 binding

Sig.: significant; IL: interleukine; RANTES: Regulated on Activation Normal T-cell Expressed and Secreted; MCP-1: Monocyte Chemotactic Protein 1; R.D: Rosa Damascena; IC50: inhibition concentration where the response (or binding) is reduced by half; Ach: acetylcholine; mM: milimole; v: volume; HepG2: a human liver cancer cell line; MCF7: a breast cancer cell line; DPPH: 2,2-diphenyl-1-picrylhydrazyl; ABTS: 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid); µg: microgram; NO: nitric oxide; ONOO: Peroxynitrite GAE: gallic acid equivalents; QEE: quercetin equivalents; AA: Ascorbic acid; MIC: minimal inhibitory concentration; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; ACE-1: angiotensin I-converting enzyme; UPLC-ESI–MS: ultra-performance liquid chromatography coupled with electrospray ionization- mass spectrometry; gp120: an HIV antigen; CD4: a glycoprotein found on the surface of immune cells; HeLa: human cervical cancer cell line; Vero: normal African green monkey kidney epithelial cell line; SI: selectivity index (IC50 normal cell/IC50 cancer cell); mm: milimeter.

cell lines. Hagag et al. presented the antimutagenic activity at 10 µg/ml dosage for concrete and absolute rose oils. They also reported an accepted active inhibition concentration for these anticancer extracts, safe for human lymphocyte cells. Since they performed gas chromatography coupled with a mass spectrometer analysis, high levels of phenyl ethanol along with other phenolics were introduced as responsible ingredients.[50] In Rezaie-Tavirani's study, the contradictory effects of water soluble and non-soluble phases of *R. damascena* Mill. essential oil was noted. The evaporated phase inhibited both the human colon cancer cell line and human fibroblast cells. However, the water soluble parts of the essence in high volumes induced growth in both cell types, but lower extract volumes (2 or 3 µl) acted as a potent growth factor for human fibroblast cells without considerable effect on the cancer cell line.[52]

3.1.5. Neuroprotection and memory enhancement

Mizuno et al. showed the neuroprotective effect of *R. damascena* Mill. essential oil in an *in vitro* system of genetically manipulated cells (GT1–7) (immortalized hypothalamic neurons). The essential oil increased neuronal viability against hydrogen peroxide and aluminium.[53] In Awale's study, a chloroform extract acted as a nerve growth factor and stopped the Alzheimer's model of neuronal atrophy.[25] Jazayeri and his colleagues also reported the inhibition of acetylcholinesterase activity of the hydroalcoholic extract of this plant representing its pharmacologic benefits in memory related disorders, such as dementia.[54] These studies suggested the antioxidant[53] and nerve growth factor[25] properties of the plant.

3.1.6. Gastrointestinal effects

Four studies have been identified with conflicting effects of *R. damascena* Mill. in the GI tract. Sadraei et al. investigated the effects of a hydro-alcoholic extract obtained by percolation using 80% ethanol. They observed its stimulatory effects on ileum smooth muscle contractions which was unrelated to the isolated ions when added at microgram concentrations, but higher doses in milligrams inhibited ileum tensions in a dose dependent manner. The authors suggested the presence of different components acting inconsistently.[55] In another study, they presented the isolated geraniol and citronellol with much stronger ileum relaxation activity than the essential oil itself.[56] Other studies confirmed the stimulation of β-adrenergic, opioid receptors and voltage-dependent calcium channels for ileum contractions inhibition in guinea pigs.[57] and muscarinic receptors for ileum movements stimulation in rats[22] with almost same doses of hydro-alcoholic extracts.

3.1.7. Cardiac effects

Boskabady et al. reported the dose dependent ionotropic and chronotropic effect of *R. damascena* Mill. hydro-alcoholic extract from 0.25 to 1.0 mg% concentration on guinea pig heart along with inhibiting propranolol effects. They also declared that the contractile effect (ionotropism) was greater than the increase in heart rate (chronotropism).[58] In Kwon's study using isolated flavonoids from the plant buds in ethyl acetate solvent, a strong inhibitory activity of all isolated flavonoids except one, against the key enzyme of cholesterol synthesis (HMG-CoA reductase) was detected. That exceptional fraction named cyanidine-3-*O*-beta-glucoside significantly inhibited one of the key enzymes related to hypertension; Angiotensine Converting Enzyme-1 (ACE-1).[24] Kwon's group concluded their study on the cardiac protective effect of the plant bioactive phenolics due to inhibition of the enzymes related to atherosclerosis and hypertension.

3.1.8. Cosmetic properties

Tabrizi et al. reported the effective absorption of UV radiation of *R.*

Table 2
Animal studies on *Rosa damascena* Mill.

First author/year	Targets	Extract	Dose/Duration/Route of administration	Main Outcome	Adverse effects (toxicology)/biologic effect
Karimi et al. (2016)[71]	Rats	Ethanolic Extract	3 ml of 1% and 5% concentration administered once into the abdominal cavity after laparotomy	Compared to controls that received distilled water, sig. lower Canbaz scale of adhesion, severity of fibrosis and inflammation with 1% concentration	All rats treated with (5%) concentrationwere found dead/anti-inflammatory effects
Latifi et al. (2015)[72]	Rats with induced ulcerative colitis	Hydroalcoholic extract(RDHE) and volatile oil (RDVO)	2 h before colitis induction/ RDHE: oral (250, 500, 1000 mg/kg) and i.p (125, 250, 500 mg/kg), RDVO: oral (100, 200, 400 µl/kg)/4d	Compared to controls treated with vehicle, Sig. reduction of all indices of colitis and decline in MPO activity with all oral doses and lowest i.p dose of RDHE and lowest dose of RDVO	Increasing i.p. dosage led to death at the dose of 500 mg/kg/Anti-inflammatory effects
Kim et al. (2015)[73]	Wounded mice	Rose placenta extract	(250 µg) (1 µg/µL)/injected once subcutaneously at four edges and base of the wound	Compared to controls treated with normal saline, sig. smaller wounds after 10d. Sig. expression increase of VEGF and EGF, besides effective decrease of TGF-β1 on day 2. Vessel density increased on the last dates of 10 days10 days	No adverse effect/wound healing promotion by increasing EGF release.
Baniasad et al. (2015)[76]	Rats (normotensive)	Hydro-alcoholic extract	(250, 500, and 1000 mg/kg) once/i.p	Compared to controls treated with saline, Sig. decrease of the SBP and MAP, dose dependently. no sig. effect on heart rate	nr./Hypotensive effects without affecting heart rate.
Esfandiary et al. (2015)[65]	Amyloid-β-induced rats	Standardized methanolic extract: 548.89 ± 20.23 - mg/100 g of the total standard quercetin (0.55% w/w).	Daily (300,600,1200 mg/kg)/ 30 d/oral	Compared to controls with saline, sig. dose dependent improvement in the spatial and long-term memories with middle and high doses	Median lethal dose (LD50) was 1200 mg/kg/reverse of memory abnormalities in a rat model
Esmaeili et al. (2015)[77]	Mice infected by Plasmodium berghei	Methanolic extract	Daily doses of(10 mg/Kg)/ i.p/4 days.	Compared to untreated controls, sig. reduction of parasitemia by 57.7%	No sig. cytotoxicity (IC50 > 100 µg/ml)/Antiplasmodial activity in mice
Homayoun et al. (2015)[61]	(PTZ)- induced rats	Hydro-alcoholic extract	Daily Pretreatment with (50, 100, and 200 mg/kg)/1 wk/ oral	Compared to controls treated with saline, sig. prolongation of seizures latency, reduction of the frequency and amplitude of burst discharges, and inhibition of dark neurons production in hippocampus	nr./Anticonvulsant and neuroprotective effects on rat hippocampus.
Mohammadpour et al. (2014)[64]	Scopolamine-induced rats	Hydro-alcoholic extract	Daily (50,250 mg/kg)/2 wk/ oral	Compared to controls treated with saline, sig. shorter traveled distance and time latency and longer time spent in target quadrant and sig. increase of thiol levels in hippocampal and cortical tissues by both doses. MDA levels decreased	nr./protection effect against brain tissue oxidative
Esfandiary et al. (2014)[66]	Amyloid-β1 induced Wistar rats	Standardized methanolic extract: 548.89 ± 20.23 - mg/100 g of the total standard quercetin (0.55% w/w).	Daily (300, 600, and 1200 mg/kg)/30d/oral	Compared to controls treated with normal saline, sig. improvement of spatial learning and memory, adult neurogenesis and synaptic plasticity enhancment, all in a dose-dependent manner	nr./upregulated the gene expression of neurotrophic factors
Abbasi Maleki et al. (2013)[67]	Morphine dependent mice induced by i.p injection	Essential oil	(5%, 2% and 40%) in normal sterile saline/i.p/30 min before administration of naloxone	Sig. dose dependent reduction of morphine withdrawal signs compared to controls treated with normal saline in terms of number of jumps, grooming, teeth chattering, rearing, climbing, wet dog shakes and writhing except diarrhea.	nr./alleviation of morphine withdrawal signs probably due to flavonoids inducing GABAergic activity
Joukar et al. (2013)[75]	High-fat diet induced rabbits	Methanolic extract	Daily (1.5 g/kg of diet)/45 d/ oral	Compared to controls treated with saline, sig. increase of left ventricular systolic and diastolic pressures and atherogenic indices (TC/HDL, LDL/HDL) Compared to high fat diet alone treated group sig. decrease in LDL levels	nr./positive inotropic effect
Nazıroğlu et al. (2013)[70]	Depression induced rats by chronic mild stress	Absolute Rose oil	Daily oral (1.5 ml/kg) or 15 min vapor inhalation (0.15 ml/kg)/28 days	Compared to controls treated with saline, inhalation induced sig. decrease in lipid peroxidation levels and modulated antioxidant vitamins A, C, E and β-carotene upregulations in the cerebral cortex in depression	nr./Beneficial antideppressive effects by protection against oxidative stress probably due to the major flavonoid components: (citronellol (33.74%), geraniol (24.85%) and nerol (10.77%))
Saxena et al. (2012)[78]	Acetaminophe-n-induced oxidative stress in rats.	Aqueous extract	Daily (250, 500, and 1000 mg/kg)/oral/Full text not found	Compared to controls treated with saline, sig. dose dependent retrieve of all toxic induced biochemical parameters (transaminases, s alkaline phosphatase, LDH, albumin, bilirubin, urea, creatinine in serum and hepatic lipid peroxidation, glutathione levels, adenosine triphosphatase and glucose-6-phosphatase activity in liver) along with histopathologic	nr./Hepatoprotection from acetaminophen–induced toxicity in rats likely through antioxidant activities.

(continued on next page)

Table 2 *(continued)*

First author/year	Targets	Extract	Dose/Duration/Route of administration	Main Outcome	Adverse effects (toxicology)/biologic effect
				hepatoprotection	
Gholamhoseinia et al. (2012)[74]	Diet induced Hyperlipidemic rabbits	Methanolic extract	Daily(1.5 g/kg of hyperlipidemic diet)/oral/ 45d.	Compared to hypercholesterolemic group without treatment,moderate decreases in TC, TG, LDL-C levels and plaques formation and increase in HDL-C levels	nr./Moderate hypolipidemic and anti-plaque formation effects
Schriner et al. (2012)[79]	*Drosophila melanogaster*	Aqueous extract	5 mg/ml mixed in a yeast solution every two days/2 wk	Compared to flies fed a control diet, both mean and maximum lifespan increased, oxidative stress protection mainly in females, survival increase in both sexes when exposed to reduced iron but with increased heat stress sensitization (survival at 37 °C), heat shock proteins down-regulation at 25 °C and after heat shock (4 h at 37 °C)	nr./Fruit fly lifespan extention by protecting against iron, decrease in heat shock proteins expression
Hosseini et al. (2011)[63]	(PTZ)-induced mice for seizures	Aqueous/ ethanolic/ chloroformic extract	Aqueous extract (100, 500 and 1000 mg/kg)/ethanolic extracts (100, 500 and 1000 mg/kg)/chloroformic extracts (100, 500 and 1 000 mg/kg)/i.p before PTZ injection	Compared to controls treated with normal saline, aqueous extracts in all doses and ethanolic ones in higher doses showed sig. anticonvulsant effect by increasing both MCS and GTCS latencies. chloroformic extracts did not show any significant effect	compared to controls no sig. differences in mortality rate/sig. anticonvulsant effect in mice
Hajhashemi et al. (2010)[68]	Mice	Hydroalcoholic Extract and Essential Oil	Hydroalcoholic Extract (250, 500 and 1000 mg/kg) or essential oil(100, 200 and 400 µl/kg)/oral/30–60 min before different procedures	Compared to controls treated with saline the sig. decrease in the writhing responses induced by an i.p injection of acetic acid and potent analgesic effect in both phases of formalin test but not in light tail flick test by hydroalcoholic extract. the higher dose showed sig. reduction of carrageenan-induced paw edema. The essential oil showed no effect.	nr./sig. analgesic and anti-inflammatory effects of the Hydroalcoholic extract
Gholamhoseinian and Fallah (2009)[81]	Normal and diabetic (STZ induced) rats	Methanol extract	Once(100–1000 mg/kg)/oral	Compared to untreated controls sig. dose dependent decrease in blood glucose after maltose loading in normal and diabetic rats was detected. Also sig. α-glucosidase inhibition with a noncompetitive manner comparable to acarbose	nr./sig. anti-diabetic effect by probably due to suppressing carbohydrate absorption from the intestine
Ramezani et al. (2009)[62]	Rats with induced amygdala kindling seizures	Essential oil	Once(750 and 1000 mg/ kg)/ i.p/30 min before a daily kindling stimulation.	Compared to controls treated with a neutral solvent sig seizure stages development retardation and improvement of the ability to counteract kindling acquisition	nr./anti- epileptiform seizure activity probably due to the flavonoids act via $GABA_A$ receptors
Jafari et al. (2008)[80]	*Drosophila melanogaster*	Aqueous extract	Daily (1, 1.5, and 2 mg/ml) of rose powder in yeast/4 wk	Compared to controls only exposed to yeast, sig. decrease in mortality rate in both sexes without common confounders of anti-aging properties (decrease in fecundity or metabolic rate)	nr./anti-aging effect probably due to antioxidant properties
Rakhshandah et al. (2006)[69]	Mice	Ethanolic, aqueous and chloroformic extracts	(100, 500 and 1000 mg/kg)/ i.p/30 min before pentobarbital injection	Sig. increase in pentobarbital induced sleeping time comparable to diazepam by the ethanolic and aqueous extracts in 500 and 1000 mg/kg doses The chloroformic extract had no hypnosis	nr./hypnotic effect of ethanolic and aqueous extract

R.D: Rosa Damascena; Sig.:significant; g: gram; i.p: intra peritoneal; MPO: myeloperoxidase; d:day; LD50: median lethal dose; EGF: epidermal growth factor; VEGF: vascular endothelial growth factor; PTZ: pentylenetetrazol; IC50: Inhibition Concentration where the response (or binding) is reduced by half; TC: total cholesterol; TG: triglyceride; LDL-C: low density cholesterol; HDL-C: high density cholesterol; TGF-β1: transforming growth factor-β1; SBP: systolic blood pressure; MAP: mean arterial pressure; MDA: malondialdehyde; min: minute; LDH: lactate dehydrogenase; MCS: minimal clonic seizure; GTCS: and generalized tonic-clonic seizure; STZ: streptozotocin; wk: week; nr.: not reported.

damascena Mill. hydro-alcoholic and ethyl acetate extracts. They also presented higher flavonoids in the ethyl acetate extract.[27] The anti-acnea effect of the essential oil, by potent antibacterial properties against *P. acnes* has been reported.[42] In Solimine's study, an anti-tyrosinase activity 10 times more potent than kojic acid, as an anti-hyperpigmentation substance, was presented by a polyphenolic fraction isolated from rose oil distillation waste water.[59]

3.1.9. Respiratory effect

Boskabady et al. showed the relaxant effect of *R. damascena* Mill. on guinea pig's trachea. Both the ethanolic and oil extracts acted as well as theophylline, but the essential oil was much more potent.[60]

3.2. Animal studies

3.2.1. Neurologic effects

The majority of animal studies have investigated the various neurological effects of *R. damascena* Mill., such as:

Anti-convulsant effect: in Homayoun's study, one week oral pretreatment of the hydro-alcoholic extract from 50 to 200 mg/kg showed prominent anti-seizure effects in a rat model.[61] The anticonvulsant effect of the intraperitoneal administration of its essential oil on rats[62] and oral intake of both aqueous and ethanolic extracts on mice were also considerable.[63]

Neuroprotection effects: Homayoun et al. presented the inhibition of dark neurons production in the hippocampus by oral intake of the hydro-alcoholic extract in a rat model.[61] In Mohammadpour's study, the brain of scopolamine induced rats was protected from oxidative

Table 3
Human studies on *Rosa damascena* Mill.

First author/year	Study type/Jadad score	Participants	Product	Dose/Duration/Route of administration	Study groups	Main Outcome	Adverse effects/comments
Farnia et al. (2017)[86]	Double-blind RCT/5	50 male patients with opium use disorder under MMT	Rose oil (Barij Essence Co.)	Daily oral intake of 2 ml in the morning/8wk	I: product C: placebo	Compared to controls, decrease of sexual dysfunction and increase of testosterone serum levels but not consistently	nr./R.D oil improved sexual function and increased serum testosterone levels in patients under MMT
Bikmoradi et al. (2016)[20]	Single-blinded RCT/2	50 patients with second- and third-degree burn wound, mean age: (33.2 ± 10.6) years in I group and (34 ± 12.4) years in C group.	R.D essence 40% in distilled water	Daily 20 min. Inhalation of 5 drops/ 30 min before dressing/ 2 d	I: extract C:distilled water	Compared to controls, sig. decrease in pain intensity based on VAS at 15 and 30 min after the intervention ($P < 0.05$).	nr./aromatherapy with R.D essence could potentially relieved the pain after dressing burn wounds
Shirazi et al. (2016)[33]	Double-blind RCT (parallel groups)/2	120 women with pregnancy-related low back pain with 18–35 years	Rose oil (in the carrier of almond oil)	Topical usage of 7 drops of oils for 100 cm2 of the painful part of skin without massage/2 times per day/4 week	I: extract C1:placebo (almond oil) C2:no intervention	Compared to controls sig. decrease in pain intensity based on VAS ($P < 0.001$) and sig. effect on functional ability compared to C2, but not to C1	Mild allergic rhinitis in one patient in the extract group/Topical rose oil exerted potential low back pain relief
Aghagoli et al. (2016)[84]	Double-blind RCT/2	60 preterm neonates	R.D distillate (10%) (Barij Essence Co.)	Daily aromatherapy with two drops (0.1 cc)/ in second day of birth, in any 3 h for 12 h/3d	I: product C: distilled water	Compared to controls sig. decrease in number of apnea attacks, bradycardia rates and SpO2 reductions in each day and sum of three days ($P = 0.001$)	nr./R.D aromatherapy had beneficial effects for premature neonates apnea besides routine treatment
Farnia et al. (2015)[34]	Double-blind RCT/5	50 female patients (mean age: 34 years) suffering from MDD and SSRI–ISD	Rose oil (Barij Essence Co.)	Daily oral intake of 2 ml in the morning/8wk	I: product C: placebo	Compared to placebo, sexual score increased over time but not significantly. No change in deppressive symptoms. Self reports of decrease in pain in the extract group	nr./modest effects on female sexual function suffering from both MDD and SSRI-ISD
Farnia et al. (2015)[85]	Double-blind RCT/5	60 male patients (mean age:32 years) suffering from MDD and SSRI-I SD	Rose oil (Barij Essence Co.)	Daily intake of 2 ml in the morning/oral/8wk	I: product C: placebo	Compared to placebo, sexual function improved significantly and symptoms of depression reduced over time	nr./ameliorates sexual dysfunction and depression in male patients suffering from both MDD and SSRI-I SD
Marofi et al. (2015)[32]	RCT/1	64 post-operative, children aged (3–6) years	R. D essence	Aromatherapy for 30 min of one to two drops at 30 cm from the head at postoperative ward arrival and then 3, 6, 9, and 12 h after surgery	I: product C:standard sweet almond oil.	After each time of aromatherapy and at the end of trial, the pain score based on (TPPPS)was significantly reduced compared to controls ($P < 0.05$)	nr./Remarkable adjunctive effects on reducing postoperative pain in children
Bani et al. (2014)[35]	Double-blind RCT (Cross-over study)/5	92 single student girls aged (18–24) years with Dysmenorrhea (pain score: 5–8 in VAS)	R. D fruit ethanol extract	One capsule of 200 mg extract/QID at first 3 days of menstruation/ Oral/in two continued menstrual cycles	I: extract C: Mefenamic Acid(250 mg/QID)	No sig. difference between the average of pain intensity based on VAS between two groups($P = 0.22$)	No side effects/Pain relief effect comparable to Mefenamic acid in primary dysmenorrhea
Igarashi et al. (2014)[87]	RCT/1	20 female university students (mean age: 22.5 ± 1.6 years)	Rose essential oil	Aromatherapy with 90 s olfactory stimulation by impregnated air	I1,2:(rose/ orange essential oils) C: unimpreg-nated air	compared to controls sig. decrease of oxyhemoglobin concentration in the right prefrontal cortex and increase of "comfortable, relaxed and natural" self feelings reports ($p < 0.05$)	nr./olfactory stimulation by rose or orange oil induces physiological and psychological relaxation effects.
Gharabaghi et al. (2011)[82]	Double-blind RCT (parallel groups)/2	92 patients undergoing elective cesarean section with (19–38 years)	Rose fruit alcoholic extract	Capsule of 800 mg extract/oral/15 min before spinal anesthesia	I: extract C: starch	Total dosage of analgesics and the severity of pain based on VAS at any time were significantly lower than controls ($P = 0.001$)	No side effects on newborns and their breast feeding in both groups/ rosehip extract can be used in elective surgical patients as an alternative analgesic
Hoseinpour et al.	Double-blind	50 patients with	R. D aqueous	Mouthwashing/2 week	I: extract	Compared to controls,	Full text not found/

(continued on next page)

Table 3 *(continued)*

First author/year	Study type/Jadad score	Participants	Product	Dose/Duration/Route of administration	Study groups	Main Outcome	Adverse effects/comments
(2011)[83]	RCT/Full text not found	recurrent aphthous stomatitis	extract		C: placebo	sig. improvements on days 4 and 7 for all parameters(pain, size, and number of ulcers)	effective in recurrent aphthous stomatitis for anti-inflammatory and antinociceptive properties
Hongratanaworakit et al. (2009)[88]	Single- blinded RCT/2	40 healthy volunteers with (18–24) years, (20 female and 20 male)	R.D essential oil	1 ml of a 20% (w/w) solution of rose oil in sweet almond oil/5 min self massage on lower abdomen with eliminated olfactory stimulation	I: R.D essential oil C: pure sweet almond oil	Compared to controls sig. decreases of autonomic arousal (breathing rate, blood oxygen saturation and SBP) and increases in self reports of calmness, relaxation and less alertness ($p \leq 0.03$). No sig. effect on DBP, PR, subjective mood, attentiveness and vigor	nr./Relaxing effect of transdermal absorption of rose oil

Sig.: significant; I: intervention; C: control; R.D: Rosa Damascena; RCT: Randomized Controlled Trial; d: day; h:hour; MMT: methadone maintenance therapy; MDD: Major Depressive Disorders; VAS: Visual Analogue Scale; TPPPS:Toddler Preschooler Postoperative Pain Scale; SpO2: peripheral capillary oxygen saturation; SSRI–ISD: selective serotonin-reuptake inhibitors induced sexual dysfunction; ml: milliliter; min: minutes; QID: in latin: quater in die(4 times a day); SBP: systolic blood pressure; nr: not reported.

damage.[64]

Memory enhancement: Esfandiary and his colleagues reported significant dose dependent memory improvements by daily oral intake of 600 and 1200 mg/kg for one month of a standardized methanolic extract in a rat model of Alzheimer's disease.[65] Using the same method, another study presented a neurogenetic effect by influencing gene expressions.[66]

Relaxant and analgesic effects: The intraperitoneal usage of different concentrations of the essential oil prominently reduced morphine withdrawal syndrome in mice.[67] In Hajhashemi's study, the oral intake of 250–1000 mg/kg of a hydroalcoholic extract potentially decreased pain in mice models.[68]

Hypnotic effect: In Rakhshandah's study, 500 and 1000 mg/kg of different extract types were injected 30 min before pentobarbital sleeping induction in mice. Both the ethanolic and aqueous extracts increased the sleeping time as well as diazepam.[69]

Anti-Depression effect: Naziroglu and his colleagues tested the effect of rose oil inhalation therapy in a depression induced rat model. They showed that vapor inhalation, not oral intake, prominently decreased peroxidation of lipids and increased the levels of antioxidant vitamins in the cerebral cortex.[70]

3.2.2. *Anti-inflammatory effects*

four studies investigated the inflammation response by prescription of different extracts of *R. damascena* Mill.[68,71–73] The subcutaneous injection of 250 µg Rose placenta in wounded mice significantly increased related growth factors and accelerated the healing process.[73] Latifi and his colleagues showed remarkable amelioration of colitis indices by oral pretreatment of both hydroalcoholic and volatile oil extracts in rats. They also reported antioxidant effect against myeloperoxidase enzyme.[72] In another study, the usage of 3 ml of an ethanolic extract(1%,5%) into the cavity of rats abdomen significantly

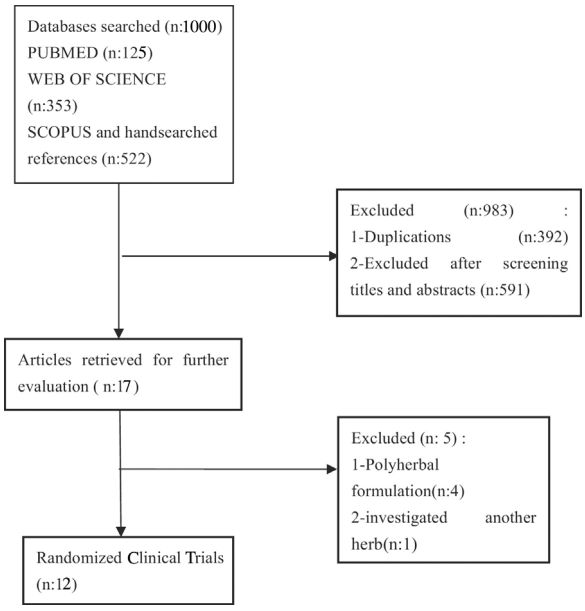

Fig. 1. The flowchart of the literature review and study selection.

reduced fibrosis and adhesions after laparotomy.[71]

3.2.3. Cardiac effects

In Gholamhoseinian's study, the daily oral administration of 1.5 g/kg *R. damascena* Mill. methanolic extract in diet induced hyperlipidemic rabbits for 45 days, exhibited a moderate decrease in atherosclerotic plaques formation, besides lipid profile improvements.[74] In another study with the same method, a significant increase in the left ventricular systolic pressure was recorded in hyperlipidemic rabbits but not in normal ones.[75] In Baniasad's study, the intraperitoneal infusion of 250–1000 mg/kg of hydroalcoholic extract dose dependently decreased the arterial pressure without affecting the heart rate in normal rats.[76]

3.2.4. Antimicrobial effect

In one study, the intraperitoneal administration of 10 mg/kg of *R. damascena* Mill. methanolic extract in infected mice significantly reduced the parasitemia of *Plasmodium berghei*.[77]

3.2.5. Antihyperlipidemic effects

In Joukar's study, 45 days oral intake of the methanolic extract of *R. damascena* Mill., 1.5 g/kg of diet per day exhibited conflicting results in hyperlipidemic rabbits.[75] Rabbits fed a high fat diet plus the extract had considerable lower LDL cholesterol levels than the group fed with a high fat diet alone but the atherogenic indices did not decrease considerably.[75] A previous study utilized the same method and showed moderate but insignificant improvements in the lipid profile and plaques formation.[74]

3.2.6. Antioxidant effects

Numerous studies have presented the antioxidative activity of *R. damascena* Mill.[64,70,72,78–80] but some have been medically considered as follows: Hepatoprotective effect: In one study, the daily oral administration of 250–1000 mg/kg of the aqueous extract, dose dependently reversed the biochemical, enzymatic and histopathological toxic effects of acetaminophen induced oxidative damage on rats liver.[78] Anti-aging effect: Schriner et al. studied the effect of 5 mg daily oral intake of the aqueous extract on a fruit fly species for 2 weeks. They observed increased mean lifespan, down-regulation of heat shock proteins and antioxidant effects.[79] In another study with the same method but lower dosage, the anti-aging effect was shown without decrease in fecundity or metabolism; common confounders of the anti-aging effect.[80]

3.2.7. Antidiabetic effect

In a study on both normal and diabetic rats, once oral intake of 100–1000 mg/kg of methanolic extract of *R. damascena* Mill. significantly reduced postprandial glucose levels dose dependently. The extract showed intensive noncompetitive α-glucosidase inhibitory effect comparable to acarbose.[81]

3.3. Human studies

Totally, twelve clinical studies on various effects of mono preparations of *R. damascena* Mill. were identified. All were designed as randomized controlled trials, such that seven studies were double blinded.

3.3.1. Analgesic and antinociceptive effect

It was found that six studies investigated the analgesic property of *R. damascena* Mill. Bikmoradi et al. observed a preemptive inhalation therapy of (40%) essential oil on 50 patients with deep burn wounds. They reported considerable pain relief, 15 and 30 min after wound dressing when patients had received aromatherapy.[20] Another preemptive study on 92 candidates of cesarean operation before routine procedures onset, showed significant lower pain scores in patients who had received capsules of rosehip extract compared to placebo controls without any adverse effect on newborns.[82] A postoperative study on children from 3 to 6 years also reported efficient pain relief with essential oil aromatherapy.[32] In Bani's study on 92 female students, the daily oral intake of 800 mg of fruit ethanolic extract at the first three days of the menstrual period relieved primary dysmenorrhea comparable with mefenamic acid.[35] Shirazi et al. showed that in 120 pregnant women, the topical usage of Rose oil two times per day for one month, significantly relieved low back pain compared to groups who received almond oil or no treatment.[33] In a study on patients suffering from recurrent oral aphthous, 2 weeks mouthwashing with the aqueous extract resulted in significant improvements on pain and inflammation indices such as the size and number of ulcers.[83]

3.3.2. Respiratory effect

Aromatherapy of preterm neonates at the first days of life with a 10% distillate of *R. damascena* Mill. significantly decreased the apnea attacks compared to the controls.[84]

3.3.3. Anti-deppression and sexual functions effects

In two separate studies, Farnia et al. showed the effects of daily oral intake of 2 ml rose oil for two months. It reduced depression symptoms over time but significantly improved sexual function in depressed men suffering from sexual dysfunction induced by selective serotonin-reuptake inhibitors (SSRI).[85] Besides, they concluded that rose oil had no effect on depression in women but modestly increased their sexual function scores.[34] In another study, the oral intake of rose oil by patients with opium use disorder under methadone maintenance therapy, decreased sexual dysfunction and increased serum testosterone levels over two months.[86]

3.3.4. Relaxing effects

Igarashi et al. revealed the effects of aromatherapy using an artificial air chamber for 90 s and a 24-L odor bag which was impegrenated by 0.2 μl of *R. damascena* essential oil. They recorded a significant decrease of oxyhemoglobin concentration in the right prefrontal cortex as an index of brain activity in 20 young female students. Furthermore, considerable subjective relaxation feelings were recorded. In their study they recorded prominent psychological relaxation effects along with brain physiological changes.[87] In another study on 40 healthy male and female volunteers, five minutes self abdominal massage of 1 ml diluted essential oil (20% concentration) without olfactory sensation exhibited remarkable relaxation. It was not only exhibited by decreasing autonomic responses, but also by subjective reports.[88]

3.4. Toxicity and adverse effects

The oral administration of *R. damascena* Mill. infusion to dogs at increasing doses, up to 8 times that traditionally used in humans (1440 mg/kg/d) for 10 days, showed negligible nephrotoxic and hepatotoxic effects such as significant serum alanine aminotransferase increase in the 10th day and increase in transient serum bilirubin in day 3.[89] Esfandiary et al. studied the toxicologic effects of Damask rose methanolic extract on rats and calculated the median lethal dose (LD50) as 1200 mg/kg. Additionally, in all reviewed clinical studies, no serious side effects were noted. The only reported side effect was a mild allergic rhinitis case in the topical usage of rose oil on pregnant women.[33]

4. Discussion

To the best of our knowledge, this is the first systematic review on clinical studies of *R. damascena* Mill. to assess its effectiveness and safety. The first remarkable finding of this review is the paucity of well-designed trials assessing the great range of well-documented *in vitro* and *in vivo* pharmacological effects of *R. damascena* Mill. Of the twelve included randomized controlled trials, most had low evidence qualities

according to the Jadad scale (score ≤ 2).[90]

Six studies investigated the pain reducing effect of the plant but Bani and his colleagues presented the only high quality study. They compared the oral administration of *R. damascena* Mill. ethanolic extract versus NSAIDS and showed no significant difference between their effects in relieving primary dysmenorrheal pain.[35] Although the anti-nociceptive mechanism of *R. damascena* Mill. is not fully understood,[4] its anti-inflammatory effects have been well exhibited by various basic and animal studies.[46,47,72,73] In wound healing, the contribution of increased growth factors expression such as epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) and the decrease of pro-inflammatory cytokines by Rosa placenta extract has been shown.[73] In another animal study, the effectiveness of Damask rose hydro-alcoholic extract on healing colitis was better than its volatile oil, suggesting the structural arrangement of active components besides their quantities as major key factors for the various effects of the plant.[72] Although the inhibition of pro-inflammatory genes expression suggest the major role of polyphenolic enriched ingredients as immunomodulators, the antioxidative effect of its flavonoids such as quercetin and kaempferol, mainly found in alcoholic extracts[4,72] may also describe *R. damascena* Mill as a potent analgesic adjuvant in inflammatory states.[91]

5. Conclusion

Regarding the various broad medical effects of *R. damascena* Mill in pre-clinical studies, more human studies are expected for assessing its properties. Although the positive findings in depression, sexual function, relaxation and respiration are valuable; multiple studies representing significant analgesic and anti- inflammatory outcomes are more considerable while due to limitations such as heterogeneity and low quality methodology, they should be cautiously interpreted. In conclusion, there are promising evidences for the effectiveness and safety of *Rosa damascena* Mill in pain relief; even though conducting confirmatory higher quality clinical trials with standardized plant products is suggested to draw firm conclusions.

Conflict of interest

There is no conflict of interests.

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