ACTA SCIENTIARUM POLONORUM

Acta Sci. Pol. Hortorum Cultus, 19(3) 2020, 47–61

https://czasopisma.up.lublin.pl/index.php/asphc ISSN 1644-0692 e-ISSN 2545-1405 DOI: 10.24326/asphc.2020.3.5

ORIGINAL PAPER

Accepted: 13.06.2019

POT MARIGOLD (*Calendula officinalis* L.) – A POSITION IN CLASSICAL PHYTOTHERAPY AND NEWLY DOCUMENTED ACTIVITIES

Agnieszka Szopa✉, Marta Klimek-Szczykutowicz, Karolina Jafernik, Katarzyna Koc, Halina Ekiert

Chair and Department of Pharmaceutical Botany, Jagiellonian University, Medical College, ul. Medyczna 9, 30-688 Kraków, Poland

ABSTRACT

The flower (inflorescence, basket-type inflorescence) of marigold (*Calendulae officinalis flos*) is a well-known plant raw material in traditional phytomedicine. It has a complex chemical composition, dominated by flavonoids and terpenoids. Terpenoids are mainly represented by oleanolic acid derivatives specific for this species: triterpenoid saponins – calendulosides A–H and triterpenoid glycosides, so-called calendulaglycosides A and B. Biological activity profiles of the raw material, such as anti-inflammatory, antimicrobial, immunostimulatory and antioxidant properties, determine its use especially in the treatment of dermatological diseases. In addition to spasmolitic, hypolipemic and antidiabetic properties of this flower, scientific studies also demonstrated its cardioprotective, hepatoregenerative, pancreas-regenerating, neuroprotective and even anticancer health-promoting effects. Moreover, *C. officinalis* is used in the cosmetology and food industry.

Key words: marigold, medicinal plant, chemical composition, therapeutic properties, cosmetic application

GENERAL CHARACTERISTICS OF THE SPECIES AND POSITION IN MEDICINE

Calendula officinalis L. is a species belonging to the family *Asteraceae*, formerly *Compositae*. The name of the species – *Calendula* – comes from the Latin word *calends*, meaning the first day of each month, which is associated with the flowering periods of the plant [Basch et al. 2006, Arora et al. 2013, John et al. 2017]. *C. officinalis* is an annual or biennial herbaceous plant, reaching from 30 to 60 cm in height. Distinctive features of the plant's appearance are heterophylly (in a single individual, the lower leaves are ovoid and upper are lanceolate) and the basket-type inflorescence composed of two types of flowers (so-called ligular flowers on the external side of the inflorescence, and tubular flowers on the internal side). Typically, the inflorescences are yellow-orange, but there are also marigold cultivars with light-yellow and dark-orange flowers. The flowering period of marigold in Europe is from June to September. Importantly, all parts of the plant are covered with glandular hairs of a multicellular structure where the essential oil is produced [Arora et al. 2013, European Pharmacopoeia 9.0 2017, Farmakopea Polska XI 2017].

Natural marigolds localities are found in Europe in the Mediterranean region and the Middle East. Currently, it is a widespread and valued plant cultivated for medicinal and ornamental purposes also in other parts of Europe (the Balkans, Eastern Europe and Germany) as well as in North America [Basch et al. 2006, John et al. 2017].

Marigold inflorescence is a long-known healing raw material in folk medicine. The first written records

✉ a.szopa@uj.edu.pl

about its application date back to the 12th century [Bingen 1155]. Traditionally, it has been used externally to treat small wounds, burns and other skin problems. This application in dermatological diseases, also known today, has been the subject of previous reviews regarding *C. officinalis* [Arora et al. 2013, Leach 2008, Muley et. al. 2009, Paul et al. 2018, Preethi and Kuttan 2009, Shafeie et al. 2015].

Mature, dried marigold flowers (syn. calendula inflorescences, calendula baskets, calendula basket inflorescence) – *Calendulae flos* – are currently used as pharmaceutical raw material in official phytotherapy. A monograph with such a title is listed in the European Pharmacopoeia 9th [European Pharmacopoeia 9.0 2017]. According to pharmacopoeial guidelines, the raw material should contain more than 0.4% of flavonoids, calculated per hyperoside [European Pharmacopoeia 9.0 2017].

Calendula flower also has a positive opinion of the European Scientific Cooperative on Phytotherapy [ESCOP] and the Committee on Herbal Medicinal Products (HMPC) specifically appointed by the European Medicines Agency [EMA]. Since 2004, this raw material has been also described in a monograph entitled *Flos Calendulae* in the International Pharmacopoeia issued by the World Health Organization [WHO 2002]. The raw material has been also much longer included, since 1986, in phytotherapeutic monographs issued by German Commission E Monographs, Phytotherapy [1986].

In addition, *C. officinalis* is accepted by the European Commission as a safe cosmetic ingredient [CosIng].

BIOACTIVE COMPONENTS

Many secondary metabolites are responsible for the biological activity of *C. officinalis*. The main group are flavonoid compounds, among others, aglycones: quercetin, isoquercetin, rutinoside, narcissin, and glycosides: quercetin-3-rutinoside, isorhamnetin-3-neohesperidoside (calendoflavoside) and quercetin 3-neohesperidoside (calendoflavobioside) (Fig. 1, Tab. 1) [Arora et al. 2013, Khalid and Silva 2012]. Calendoflaside is another specific compound belonging to the flavonoids that has been isolated for the first time from the marigold's inflorescence in 1989 (Fig. 1, Tab. 1) [Miguel et al. 2016].

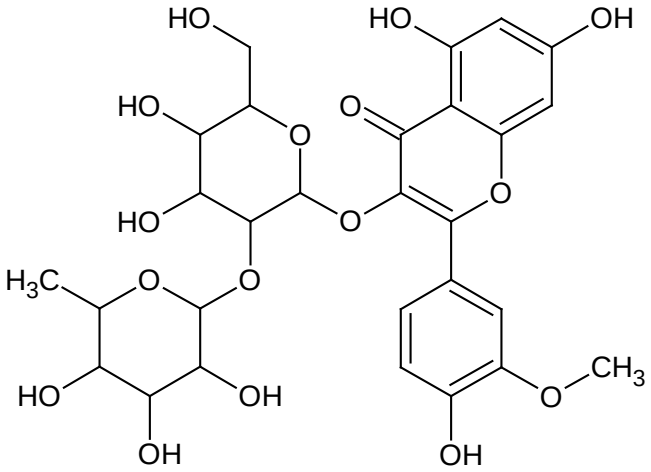
Terpenoids are an important group of secondary metabolites, which occur in the *C. officinalis* inflorescence and are responsible for its biological activity [Arora et al. 2013, Muley et al. 2009]. It is possible to distinguish in this group of compounds triterpendiol monoesters: esters of faradiol (faradiol-3-O-palmitate, faradiol-3-O-myristate, faradiol-3-O-laurate), esters of arnidiol (arnidiol-3-O-palmitate, arnidiol-3-O-myristate, arnidiol-3-O-laurate) and specific for *C. officinalis* – calenduladiol and its esters (calenduladiol-3-O-palmitate, calenduladiol-3-O-myristate) [Arora et al. 2013, Khalid and Silva 2012]. Derivatives of oleanolic acid – triterpenoid saponins: calendulosides A–H are an important, specific for *C. officinalis* compounds from the group of terpenoids (Fig. 2, Tab. 1) [Arora et al. 2013, Khalid and Silva 2012, Muley et al. 2009]. Triterpenoid glycoside derivatives of oleanolic acid, so-called calendulaglycoside A and B and their esters are also characteristic compounds that occur only in this species (Fig. 3, Tab. 1) [Grzelak and Janiszowska 2002, Ukiya et al. 2006, Wiktorowska et al. 2010, Farahpour 2014].

The presence of coumarins (esculetin, scopoletin, umbelliferone), lipids (phospholipids, glycolipids), fitosterols, aminoacids (alanine, leucine, lysine, methionine) and saccharides has been also documented in *C. officinalis* infloresences (Tab. 1) [Arora et al. 2013, Khalid and Silva 2012].

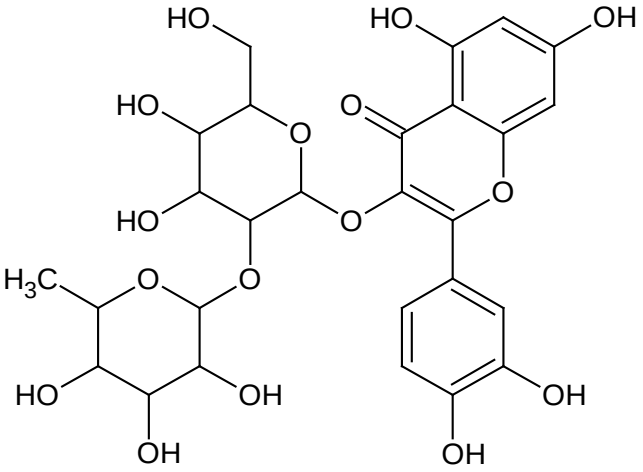
In addition, compounds from the carotenoid group: α- and β-carotene, flavoxanthin, luteoxanthin, lycopene and lutein and its derivatives were mainly isolated in the extracts of marigold flowers as well as in pollen and leaf extracts (Tab. 1) [Muley et al. 2009, Arora et al. 2013, Khalid and Silva 2012, Legha et al. 2012].

An important raw material obtained from *C. officinalis* flowers is an essential oil containing mainly terpenoid compounds from the monoterpenoid group, such as limonene, α-pinene, β-pinene, α-thujene, sabinene, *p*-cymene and sesquiterpenoids, e.g. α-humulene, α-yanglene, germacrene D and nerolidol (Tab. 2). The percentage of essential oil content in inflorescences depends on the stage of plant development. The largest production takes place during the flowering period of the plant [Muley et al. 2009, Khalid and Silva 2012, Arora et al. 2013].

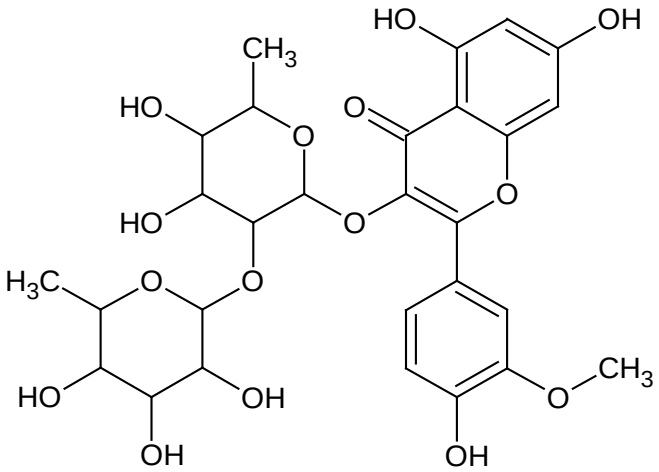
Characteristic metabolites of the family *Asteraceae* species are polysaccharides that affect the immune



isorhamnetin-3-neohesperidoside
(calendoflavoside)

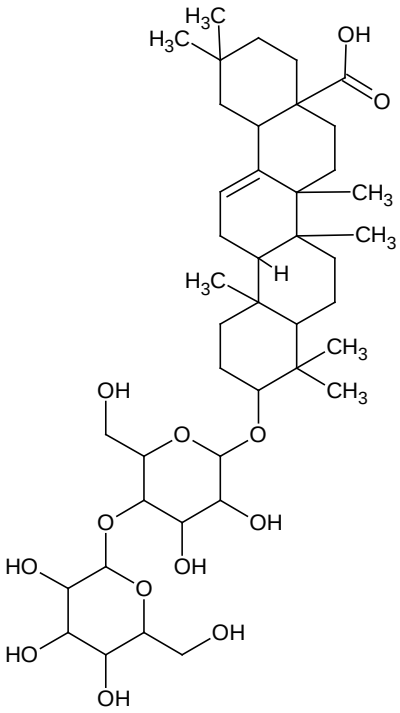


quercetin 3-neohesperidoside
(calendoflavobioside)

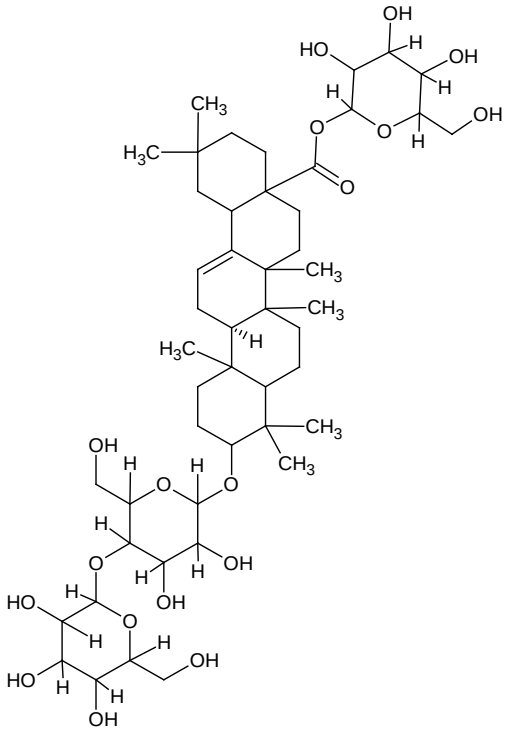


calendoflaside

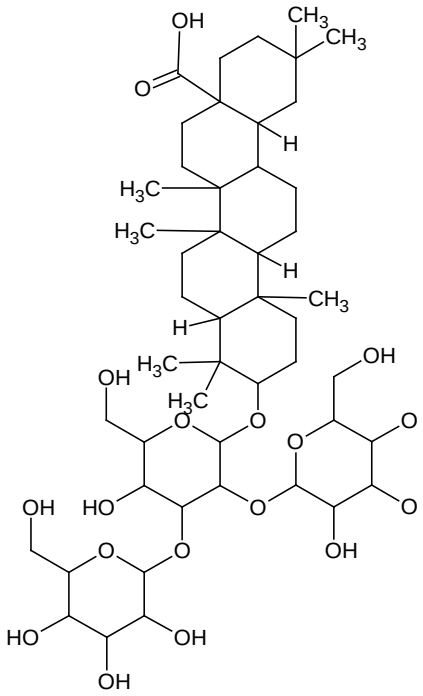
Fig. 1. Chemical structures of flavonoids specific for *C. officinalis*



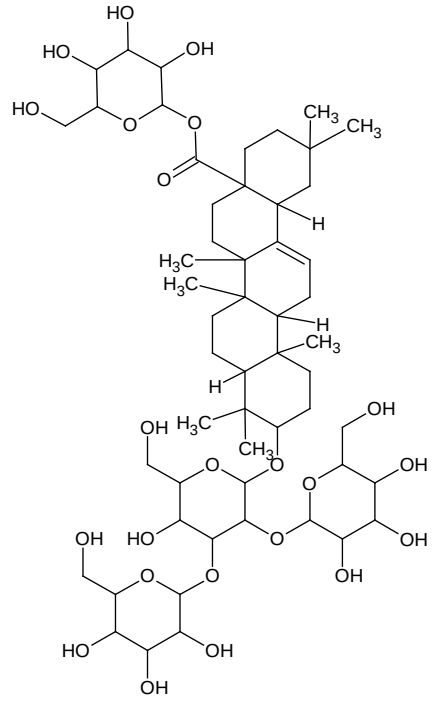
calenduloside A



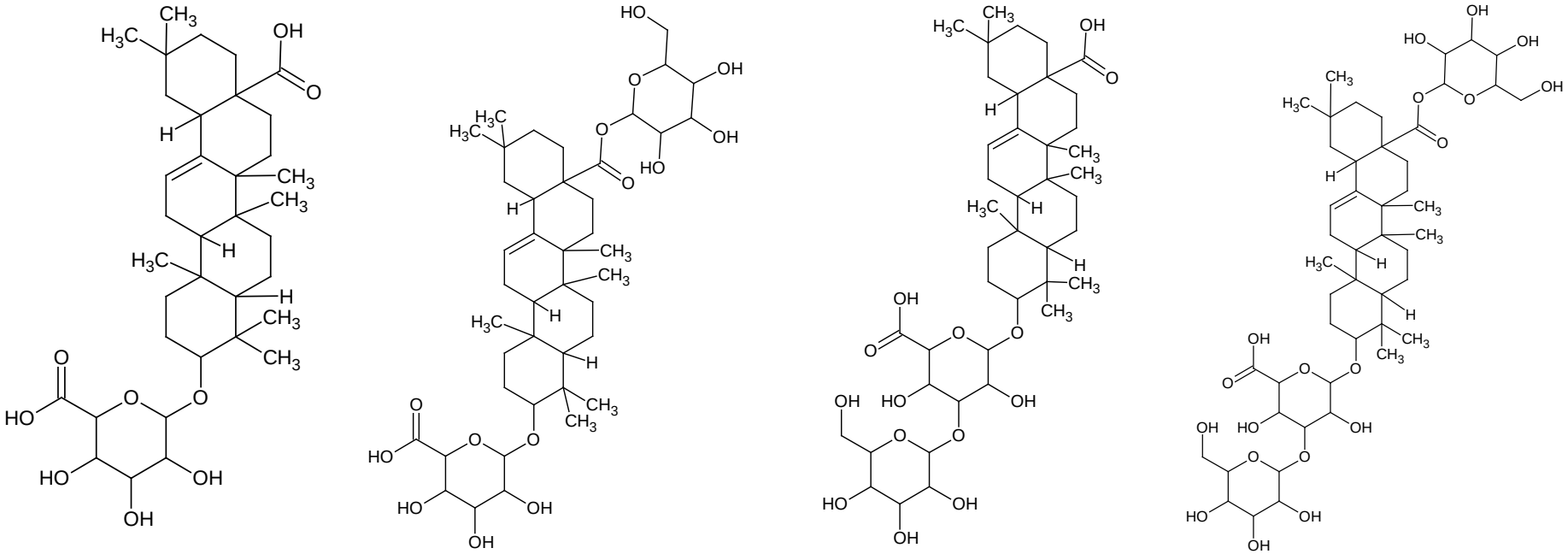
calenduloside B



calenduloside C



calenduloside D



calenduloside E calenduloside F calenduloside G calenduloside H

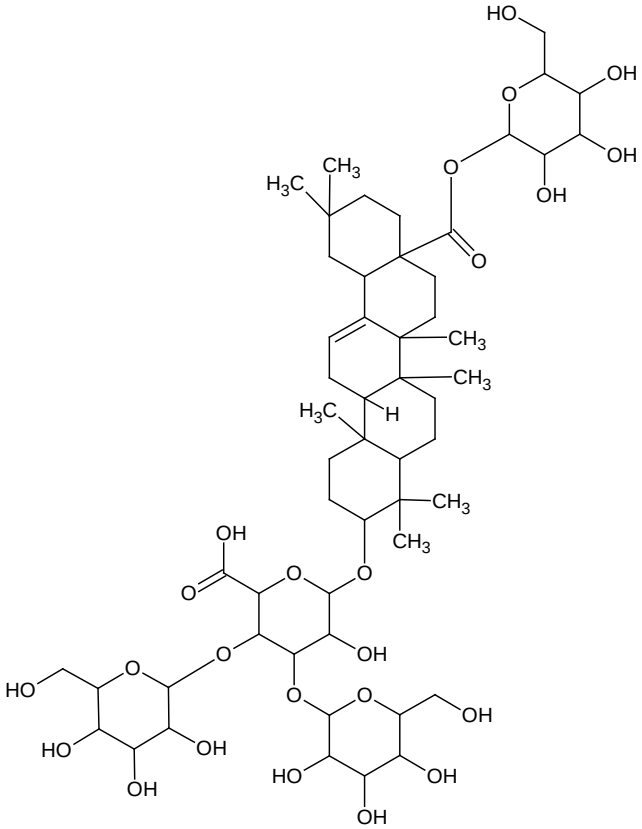
Fig. 2. Chemical structures of *C. officinalis*-specific triterpenoid saponins (oleanolic acid derivaties): calendulosides A–H

Table 1. Chemical composition of *C. officinalis*

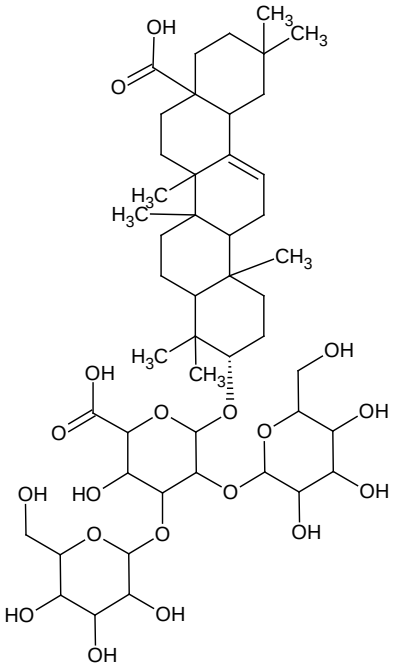
Group of secondary metabolites		Compounds	References
Flavonoids	aglycones	isoquercitrin, narcissin, quercetin, rutinoside	Ukiya et al. 2006, Kurkin and Sharova 2007, Hernández-Saavedra et al. 2016, Miguel et al. 2016
	glycosides	calendoflaside, isorhamnetin-3-neohesperidoside (calendoflavoside), quercetin 3-neohesperidoside (calendoflavobioside), quercetin-3-O-rutinoside	
Terpenoids	triterpenoids	erythrodiol, monoesters of lupeol, taraxasterol, ursadiol	Neukirch et al. 2004, Ruszkowski et al. 2005, Ukiya et al. 2006, Muley et al. 2009, Arora et al. 2013, Nizyński et al. 2015, Miguel et al. 2016, John et al. 2017
	triterpendiol monoesters	calenduladiol and its esters (calenduladiol-3-O-palmitate, calenduladiol-3-O-myristate), esters of arnidol (arnidiol-3-O-palmitate, arnidiol-3-O-myristate, arnidiol-3-O-laurate), esters of faradiol (faradiol-3-O-palmitate, faradiol-3-O-myristate, faradiol-3-O-laurate)	
	triterpenoid saponins	calendulosides A–H	
	triterpenoid glycosides	calendulaglycosides A and B and their esters: calendulaglycoside A 6-O-n-methyl ester, calendulaglycoside A 6-O-n-butyl ester, calendulaglycoside B 6-O-n-butyl ester, glucuronides A, B, C, D, F	
Carotenoids		auroxanthin, α-cryptoxanthin, α-carotene, β-carotene, β-cryptoxanthin, flavoxantin, lutein and its derivatives (9/9A-lutein, 13/13 Z-lutein), luteoxanthin, lycopene, neoxantin, 9Z-neoxantin, violaxanthin, 9Z-violaxanthin	Muley et al. 2009, Legha et al. 2012, Arora et al. 2013, John et al. 2017
Coumarins		esculetin, scopoletin, umbelliferone	Bakó et al. 2002
Lipids		fatty acids: lauric acid, palmitic acid, stearic acid, linoleic acid, glycolipids, phospholipids	John et al. 2017
Fitosterols		stigmasterol, sitosterol	Muley et al. 2009, Arora et al. 2013
Amino acids		alanine, arginine, aspartic acid, histidine, glutamic acid, leucine, lysine, methionine, phenylalanine, proline, serine, tyrosine, valine	Muley et al. 2009, Arora et al. 2013, John et al. 2017
Saccharides		arabinogalactan, neohesperidose and its derivatives, ramnoarabinogalactan	Muley et al. 2009 Arora et al. 2013
Benzofurans		calendin	Colombo et al. 2015, John et al. 2017

Table 2. Chemical composition of *C. officinalis* essential oil [Okoh et al. 2007, John et al. 2017]

	Terpenoid compounds of *C. officinalis* essential oil
Monoterpenoids	1,8-cineol, p-cymene, geraniol, limonene, ocimene, trans-β-ocimene, α-pinene, β-pinene, sabinene, α-terpineol, terpinen-4-ol, α-thujene
Sesquiterpenoids	calarene, cadina-1,4-diene, δ-cadinen, α-cubebne, germacrene D, α-humulene, α-kadinol, nerolidol, T-muurolol, epi-bicyclo-sesquiphellandrene, α-ylangene



calendulaglycoside A



calendulaglycoside B

Fig. 3. Chemical structures of *C. officinalis*-specific triterpenoid glycosides (glycosides of oleanolic acid): calendulaglycoside A and B

Table 3. Biological activity and mechanisms of *C. officinalis* effects confirmed by scientific research

Biological activity	Mechanism of action	References
Anti-inflammatory activity	inhibition of ear edema in mice induced by irritants (flower extract containing faradiol monoesters), reduction of burn swellings in rats by using a cream with the addition of ethanol flower extract, inhibition of proinflammatory cytokines (IL-1β, Il-6, TNF-α and IFN-γ) and C-reactive protein (CRP) in mice with induced inflammation by lipopolysaccharide (LPS) injection (ethanol flower extracts), reduced inflammatory bone resorption (oral administration of the flower extract), reduction of symptoms of bacterial vaginosis in women of childbearing age (cream with flower extracts), reduction of myeloperoxidase, lactate dehydrogenase and lipid peroxidase activity in rat colitis (methanol flower extracts)	Alexandre et al. 2018, Arora et al. 2013, Banakar et al. 2016, Farahpour 2014, Muley et al. 2009, Parente et al. 2012, Singh et al. 2011, Ukiya et al. 2006
Wound healing acceleration activity	increased granulation tissue formation by accelerating the metabolism of collagen, nucleoproteins and glycoproteins (flower extracts), increase in the rate of new blood vessel formation in skin wounds in rats (water flower extracts), reduction of collagenase activity (water and methanol extract from flowers and leaves), an increase in the rate of wound healing in patients with venous leg ulceration (hydroglycolic flower extracts), acceleration of healing, reduction of infection, itching, redness, pain in foot injuries in people with diabetes (cream with flower extracts), increase in the proliferation and migration of fibroblasts in human lung fibroblast cells, Swiss albino mouse fibroblast cells and human primary dermal fibroblast cells (ethanol flower extracts)	Buzzi et al. 2016, Dinda et al. 2015, Gilca et al. 2018, Lovecka et al. 2018, Nicolaus et al. 2017, Paul et al. 2018
Antibacterial activity	Gram (+) bacteria: *Actinomyces odontolyticus*, *Bacillus subtillis*, *Enterococcus faecalis, Micrococcus luteus*, *Peptostreptococcus micros*, *Staphulococcus aureus*, *Streptococcus mutans* (water and methanol flower extracts), Gram (–) bacteria: *Agrobacterium tumefaciens*, *Burkholderia glathei*, *Caphocytophaga gingivalis*, *Eikenella corrodens*, *Escherichia coli*, *Furobacterium nucleatum*, *Porphyromonas gingivalis*, *P. intermedia*, *Prevotella* spp., *Pseudomonas aeruginosa*, *P. syringae*, *Veilonella parvula*, *Vibrio cholerae* (water and methanol flower extracts)	Arora et al. 2013, Khalid and Silva 2012, Lovecka et al. 2018, Muley et al. 2009, Shankar et al. 2017, Singh et al. 2011
Antifungal activity	growth inhibition of *Candida* strains: *C. albicans*, *C. dubliniensis*, *C. glabrata*, *C. krusei* and *C. parapsilosis* (flower essential oil), growth inhibition of strains: *Geotrichum candidum*, *Microsporum canis*, *M. gypseum*, *T. mentagrophytes*, *Trichophytom rubrum* (methanol flower extracts)	Faustino et al. 2018, Khalid and Silva 2012, Lovecka et al. 2018, Saffari et al. 2017
Antiviral activity	inhibition of HIV replication (organic solvent flower extracts), inhibition of herpes and influenza virus (flower tincture), moderate inhibitory effect on Epstein-Barr virus (EBV-EA) (*C. officinalis* triterpenenoid glycosides)	Muley et al. 2009, Salehi et al. 2018, Ukiya et al. 2006
Antitrichomona activity	growth inhibition of *Trichomonas vaginalis* protozoan (components of the essential oil)	Samochowiec et al. 1979

Table 3 cont.

Biological activity	Mechanism of action	References
Antioxidant activity	reduction of superoxide and hydroxyl radicals (butanol flower extracts), increase in the concentration of reduced glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) in periodontitis in rats (aqueous flower extracts), reduction of production of reactive oxygen species (ROS) in skin cells treated with H_2O_2 (ethanol flower extracts), inhibition of lipid peroxidation in rat liver microsomes (butanol flower extracts), reduction of malondialdehyde (MDA) concentration in periodontitis in rats (water flower extracts)	Cordova et al. 2002, Farahpour 2014, Lima et al. 2017, Xuan et al. 2016
Skin brightening effect	inhibition of melanin production induced by alpha melanocyte-stimulating hormone in melanoma cells (flower ethyl acetate extracts)	Xuan et al. 2019
Spasmolytic activity	inhibition of spontaneous intestine contractions (water-ethanol flower extracts)	Arora et al. 2013, Muley et al. 2009
Antidiabetic and hypolipemic activity	reduction in blood and urine glucose levels in diabetes-induced rats (water-ethanol flower extract), restoration of normal blood and urine glucose concentration and blood lipids in diabetes-induced rats (high doses of water-ethanol flower extracts), reduction in blood glucose levels in hyperglycemic rabbits (extracts from *C. officinalis*, *Salvia officinalis*, *Glycyrrhiza glabra*, *Echinacea purpurea*), increase in liver glycogen levels in hyperglycemic rabbits (extracts from *C. officinalis*, *Salvia officinalis*, *Glycyrrhiza glabra*, *Echinacea purpurea*)	Singh et al. 2011, Aghajanyan and Trchounian 2018, Singh et al. 2011
Hepatoprotective and hepatoregenerative activity	reduction of hepatocytolysis and inhibition of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, succinate dehydrogenase and cyclooxygenases activities (water-ethanol flower extracts), increase in the activity of reduced glutathione enzymes, superoxide dismutase, catalase and increase of adenosine triphosphate content in hepatocytes in the rat model of acute hepatitis (flower extracts)	Muley et al. 2009, Singh et al. 2011, Toropova et al. 2017
Pancreas regenerating activity	increase in the production of nucleic acids, proteins, pancreatic amylase, and eduction of pancreatic oxidative stress in cells of the pancreatic parenchyma (ethanol flower extracts)	Kaur et al. 2016
Cardioprotective activity	cardioprotective effect by regulating blood pressure and flow in the aorta and left ventricle (flower extracts), reduction in the extent of myocardial infarction and cardiomyocyte apoptosis in induced ischemic disease in rats (flower extracts)	Singh et al. 2011
Neuroprotective activity	reduction of oxidative damage and striatal neuronal loss in rats with induced neurotoxicity (ethanol flower extracts)	Shivasharan et al. 2013
Antitumor activity	cytotoxic effect on cell lines: colon cancer, leukemia, melanoma and breast cancer (*C. officinalis* triterpenenoid glycosides), cytotoxic effect on Ehrlich tumor (flower extracts), inhibiting the growth of human liver cancer cells (flower extracts), inhibition of cell proliferation in human embryonic kidney (HEK 293T) and human liver cancer (HepG2) cell lines (ethanol and aqueous flower extracts)	Lovecka et al. 2018, Muley et al. 2009, Ukiya et al. 2006
Immunostimulatory activity	increase in cell phagocytosis (*C. officinalis* polysaccharide fraction)	Arora et al. 2013, Muley et al. 2009

system and sesquiterpenoid lactones with various biological activities. Marigold flowers were shown to contain polysaccharides (among others neohesperidoside and its derivatives, arabinogalactan, rhamnoarabinogalactan) with immunostimulatory properties, and sesquiterpenoid lactone – calendin (bitter constituent) [Muley et al. 2009, Arora et al. 2013, Colombo et al. 2015].

Interestingly, the sugar part of glycosidic combinations present in flowers may be formed by lactose (milk sugar), which is a huge rarity in the plant kingdom. Neohesperidose (2-O-α-L-rhamnopyranosyl-D-glucopyranose) is another characteristic disaccharide forming glycons in glycoside combinations [Muley et al. 2009, Arora et al. 2013, Colombo et al. 2015].

APPLICATION IN MEDICINE

In modern phytotherapy, as in folk medicine, *C. officinalis* flower extracts are widely used mainly in the treatment of dermatological diseases (Tab. 3) [Basch et al. 2006, Muley et al. 2009, Arora et al. 2013]. Many scientific studies on this species focused on anti-inflammatory and accelerated wound healing properties [Ukiya et al. 2006, Parente et al. 2012, Farahpour 2014, Buzzi et al. 2016, Nicolaus et al. 2017, Alexandre et al. 2018, Paul et al. 2018]. Anti-inflammatory activity is conditioned by the presence of terpenoid compounds (Fig. 2 and 3, Tab. 1 and 3), the higher the content of these compounds, the stronger the effect of the extract [Ukiya et al. 2006]. It has been proven that the use of an ointment with *C. officinalis* inflorescence extract reduces the incidence of dermatitis in people with breast cancer undergoing radiotherapy [Pommier et al. 2004]. In addition, ointments applied to skin wounds accelerate their healing by increasing epidermal epithelization [Paul et al. 2018]. New research indicates that *Calendula officinalis*-loaded poly ε-caprolactone/gum arabic nanocomposite scaffolds, when applied on wounds, increase cell adhesion and proliferation as well as have an antibacterial effect. This composition is well suited for skin regeneration [Pedram Rad et al. 2019]. Extracts of *C. officinalis* inflorescences can also be used for hard-to-heal wounds, such as venous ulcers, burns and other skin changes that are difficult to heal [Buzzi et al. 2016, Duran et al. 2005]. According to the latest research, preparations containing marigold flower extracts can be used in non-invasive and delicate therapies, difficult-to-treat plantar papules, painful hyperkeratotic changes and inflammation of the *hallux valgus* [Duran et al. 2005, Singh et al. 2011] (Tab. 3).

Extracts from *C. officinalis* inflorescences have scientifically proven antiviral, antibacterial, antifungal and antiprotozoal activity. Based on scientific research, it has been proven that *C. officinalis* extracts inhibit the activity of herpes and influenza virus, they also reduce HIV replication [Ukiya et al. 2006, Muley et al. 2009, Arora et al. 2013, Farahpour 2014, Salehi et al. 2018]. Extracts have an antibacterial effect on numerous strains of Gram (+) bacteria (incl. *Bacillus subtillis*, *Peptostreptococcus micros*, *Staphulococcus aureus*) and Gram (–) bacteria (incl. *Escherichia coli*, *Furobacterium nucleatum*, *Porphyromonas gingivalis*, *Pseudomonas aeruginosa*, *Veilonella parvula*, *Vibrio cholerae*) [Singh et al. 2011, Khalid and Silva 2012, Shankar et al. 2017, Lovecka et al. 2018, Muley et al. 2009]. In addition, it has been proven that *C. officinalis* essential oil has a stronger inhibitory effect on pathogenic fungal strains than nystatin [Khalid and Silva 2012] and inhibits the growth of the protozoan *Trichomonas vaginalis* [Samochowiec et al. 1979] (Tab. 3).

Scientific studies have demonstrated that extracts of *C. officinalis* inflorescences have antioxidant, spasmolytic, antidiabetic and hypolipemic effects [Cordova et al. 2002, Muley et al. 2009, Singh et al. 2011, Xuan et al. 2016, Lima et al. 2017] (Tab. 3). In addition, the latest report showed their pancreas-regenerating, hepatoregenerative, cardioprotective and neuroregenerative activity [Muley et al. 2009, Singh et al. 2011, Toropova et al. 2017]. Furthermore, triterpenoid glycosides found in *C. officinalis* inhibited the growth of tumor cell lines: colon cancer, breast cancer, leukemia as well as melanoma in *in vitro* tests [Muley et al. 2009, Farahpour 2014, Ukiya et al. 2006]. In addition, the *C. officinalis* saccharide group was shown to act immunostimulatory [Muley et al. 2009, Arora et al. 2013] (Tab. 3).

A detailed description of the mechanisms of extracts' biological activity and/or individual components of *C. officinalis* is presented in Tab. 3.

COSMETIC APPLICATIONS

Calendula officinalis is a popular species in the cosmetics industry, especially due to the scientifically proven anti-inflammatory, antioxidant and skin damage granulation accelerating properties [Anuradha et al. 2015]. *Calendula* is present mainly in the composition of cosmetics that have soothing, softening and regenerating effects.

Recently, an increasing popularity of preparations based on extracts from *C. officinalis* has been observed. Therefore, research focused on the cosmetic application of *C. officinalis* flower extracts is of particular interest. *In vitro* studies on skin cells with induced oxidative stress have proven that ethanol extracts from *C. officinalis* flowers have a strong antioxidant effect, and protect cells from damaging effects of UV radiation [Xuan et al. 2016]. Other studies have shown that cream with *C. officinalis* flower extract stimulates skin cell regeneration, improves elasticity, and also induces increased skin hydration, as a result of lower TEWL (transepidermal water loss) [Buzzi et al. 2016]. It has also been proven that cream with *C. officinalis* inflorescences reduces sebum secretion and has a brightening effect through the reduction of melanin content in the skin [Jadoon et al. 2015, Tundis et al. 2015]. Scientific studies have also demonstrated that the anti-aging effect of *C. officinalis* inflorescence extracts is related to the control of metalloproteinase (MMP-2 and MMP-9) secretion [Tundis et al. 2015].

Calendula officinalis oil is also applied in cosmetology. It has been proven that it has a stronger inhibitory effect on pathogenic fungal strains than nystatin [Khalid and Silva 2012] (Tab. 3). When used in emulsions, it accelerates wound healing and protects against UV radiation [Okuma et al. 2015, Lohani et al. 2018,]. In addition, the oil has a stronger antioxidant activity than geranium oil [Lohani et al. 2018].

According to Cosmetic Ingredient Database [CosIng] – an on-line database of cosmetic ingredients introduced by the European Commission – *C. officinalis*, is a species that can be used in ten different forms (Tab. 4). Interestingly, recently, the Bulgarian company Innova BM patented and introduced to the market two innovative cosmetic preparations based on *C. officinalis* cell cultures – with moisturizing, anti-aging and regenerating properties [Georgiev et al. 2018].

FOOD APPLICATION

In the past, marigold leaves were used in cuisine as a vegetable. Also today, fresh marigold flowers are added to salads. Dried flowers, as a substitute for saffron, are a spice for soups and cakes; moreover, they are used for coloring of, among others, rice, fat (margarine) and yellow cheeses. The safety of marigold flower use in food is confirmed by the European Food Safety Authority [EFSA] documentation.

SAFETY OF USE

Caution should be exercised with allergy sufferers when using or consuming preparations containing

Table 4. *C. officinalis* in the cosmetic products acc. to CosIng database

Name acc. to CosIng	Cosmetic activity
Calendula officinalis extract	skin conditioning
Calendula officinalis callus extract	skin conditioning, skin protective, emollient
Calendula officinalis flower	skin conditioning
Calendula officinalis flower extract	skin conditioning, masking, perfuming
Calendula officinalis flower oil	skin conditioning, masking, perfuming
Calendula officinalis flower water	masking, flavouring, perfuming
Calendula officinalis flower/leaf/stem juice	skin conditioning
Calendula officinalis meristem cell extract	antioxidant
Calendula officinalis seed oil	skin conditioning
Hydrolyzed *Calendula officinalis* flower extract	skin protective

marigold extracts or oil. Special care must be taken by people who are allergic to species from the family *Asteraceae* [Corazza et al. 2014, Denisow-Pietrzyk and Pietrzyk 2019]. The most common reaction is skin allergies (contact sensitization), as reported by the American Food and Drug Administration [FDA, Reider et al. 2001] and European Medicines Agency [EMA].

CONCLUSIONS

Marigold flower is currently a widely available raw material, valuable in terms of biological, medicinal, cosmetic and food properties. Research studies confirmed strong anti-inflammatory and antioxidant properties of this raw material; in addition, they demonstrated other very important effects of its biological activity, such as hepatoregenerative, cardioprotective, neuroprotective and anticancer properties.

REFERENCES

Aghajanyan, A.A., Trchounian, A.H. (2018). Antihyperglicemic properties of the herbal mixture. Chem. Biol., 52(3), 180–186.

Alexandre, J.T.M., Sousa, L.H.T., Lisboa, M.R.P., Furlaneto, F.A.C., Do Val, D.R., Marques, M., Vasconcelos, H.C., Matos de Melo, I., Leitao, R., Brito G.A.C., Goes, P. (2018). Anti-inflammatory and antiresorptive effects of *Calendula officinalis* on inflammatory bone loss in rats. Clin. Oral Investig., 22(6), 2175–2185. DOI: 0.1007/s00784-017-2308-7

Anuradha, S.N., Vilashene, G., Lalithambigai, J., Arunkumar, S. (2015). "Cosmeceuticals": An opinion in the direction of pharmaceuticals. Asian J. Pharm. Clin. Res., 8(2), 64–69.

Arora, D., Rani, A., Sharma, A. (2013). A review on phytochemistry and ethnopharmacological aspects of genus *Calendula*. Pharmacog. Rev., 7(14), 179. DOI: 10.4103/0973-7847.120520

Bakó, E., Deli, J., Tóth, G. (2002). HPLC study on the carotenoid composition of *Calendula* products. J. Bioch. Biophys. Methods, 53, 241–250. DOI: 10.1016/S0165-022X(02)00112-4

Banakar, S.M., Veerapur, V.P., Thippeswamy, B.S., Jagadeesh, N.V., Gavimath, C.C., Alshehri, Z.S. (2016). Protective effect of *Calendula officinalis* (L.) flower extract in acetic acid-induced ulcerative colitis in rats. J. Herbs, Spices Med. Plants, 22(3), 225–237. DOI: 10.1080/10496475.2016.1190952

Basch, E., Bent, S., Foppa, I., Haskmi, S., Kroll, D., Mele, M., Szapary, P., Ulbricht, C., Voa, M., Vora, M., Yong, S. (2006). Marigold (*Calendula officinalis* L.): an evidence-based systematic review by the Natural Standard Research Collaboration. J. Herb. Pharmacother., 6(3–4), 135–159. DOI: 10.1080/J157v06n03_08

Bingen, H. von (1155). Hildegard von Bingen's Physica.

Buzzi, M., Freitas, F. de, Barros Winter, M. de (2016). Therapeutic effectiveness of a *Calendula officinalis* extract in venous leg ulcer healing. J. Wound Care, 25(12), 732–739. DOI: 10.12968/jowc.2016.25.12.732

Colombo, E., Sangiovanni, E., D'Ambrosio, M., Bosisio, E., Ciocarlan, A., Fumagalli, M., Guerriero A., Harghel P., Dell'Agli, M. (2015). A bio-guided fractionation to assess the inhibitory activity of *Calendula officinalis* L. on the NF-B driven transcription in human gastric epithelial cells. Evid.-Based Complement. Altern. Med., 2, 727342. DOI: 10.1155/2015/727342

Corazza, M., Borghi, A., Gallo, R., Schena, D., Pigatto, P., Lauriola, M.M., Guarneri, F., Stngeni, L., Vincenzi, C., Foti, C., Virgili, A. (2014). Topical botanically derived products: use, skin reactions, and usefulness of patch tests. A multicentre Italian study. Contact Dermatitis, 70(2), 90–97. DOI: 10.1111/cod.12124

Cordova, C., Siqueira, I., Netto, C. (2002). Protective properties of butanolic extract of the *Calendula officinalis* L. (marigold) against lipid peroxidation of rat liver microsomes and action as free radical scavenger. Redox Rep., 7(2), 95–102. DOI: 10.1179/135100002125000325

CosIng – Cosmetic Ingredient Database. Available: https://ec.europa.eu/growth/sectors/cosmetics/cosing_en [data of access: 06.12.2018].

Denisow-Pietrzyk, M., Pietrzyk, Ł. (2019). *Asteraceae* species as potential environmental factors of allergy. Environ. Sci. Pollut. Res. 26(1), 1–11. DOI: 10.1007/s11356-019-04146-w

Dinda, M., Dasgupta, U., Singh, N., Bhattacharyya, D., Karmakar, P. (2015). PI3K-Mediated proliferation of fibroblasts by *Calendula officinalis* tincture: Implication in wound healing. Phytother. Res., 29(4), 607–616. DOI: 10.1002/ptr.5293

Duran, V., Matic, M., Jovanovic, M. (2005). Results of the clinical examination of an ointment with marigold (*Calendula officinalis*) extract in the treatment of venous leg ulcers. Int. J. Tissue. React., 27(3), 101–106.

EFSA – European Food Safety Authority. Available: http://www.efsa.europa.eu/ [data of access: 11.11.2018].

European Pharmacopoeia 9.0 (2017). European Directorate for the Quality of Medicines, Strasburg.

EMA – European Medicines Agency. Available: https://www.ema.europa.eu/ [data of access: 06.01.2019].

ESCOP – European Scientific Cooperative on Phytotherapy. Available: http://escop.com/ [data of access: 20.02.2019].

Farahpour, M.R. (2014). Antioxidant activity, antinociceptive and anti-inflammatory effects of pot marigold hydroalcoholic extract on experimental animals. Int. J. PharmTech. Res., 6(5), 1640–1646.

Farmakopea Polska XI (2017). Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych, Warszawa.

Faustino, M.V., Pinto, D.C.G.A., Gonçalves, M.J., Salgueiro, L., Silveira, P., Silva, A.M.S. (2018). *Calendula* L. species polyphenolic profile and *in vitro* antifungal activity. J. Funct. Foods, 45, 254–267. DOI: 10.1016/j.jff.2018.04.013

Georgiev, V., Slavov, A., Vasileva, I., Pavlov, A. (2018). Plant cell culture as emerging technology for production of active cosmetic ingredients. Eng. Life Sci., 18(11), 779–798. DOI: 10.1002/elsc.201800066

German Commission E Monographs, Phytotherapy (1986). Calendula flower (*Calendulae flos*) [summary of the monograph]. Available: https://buecher.heilpflanzen-welt.de/BGA-Commission-E-Monographs/0043.htm [data of access: 26.01.2019].

Gilca, M., Tiplica, G.S., Salavastru, C.M. (2018). Traditional and ethnobotanical dermatology practices in Romania and other Eastern European countries. Clin. Dermatol., 36(3), 338–352, DOI: 10.1016/j.clindermatol.2018.03.008

Grzelak, A., Janiszowska, W. (2002). Initiation and growth characteristics of suspension cultures of *Calendula officinalis* cells. Plant Cell. Tissue Organ Cult., 71, 29–40. DOI: 10.1023/A:1016553909002

Hernández-Saavedra, D., Pérez-Ramírez, I.F., Ramos-Gómez, M., Mendoza-Díaz, S., Loarca-Piña, G., Reynoso-Camacho, R. (2016). Phytochemical characterization and effect of *Calendula officinalis*, *Hypericum perforatum*, and *Salvia officinalis* infusions on obesity-associated cardiovascular risk. Med. Chem. Res., 25(1), 163–172. DOI: 10.1007/s00044-015-1454-1

Jadoon, S., Karim, S., Hassham, M., Bin, H., Akram, M.R., Khan, A.K., Malik, A., Chen, C., Murtaza, G. (2015). Anti-aging potential of phytoextract loaded-pharmaceutical creams for human skin cell longetivity. Oxidative Med. Cell. Longev., 2015, 1–17. DOI: 10.1155/2015/709628

John, R., Andrabi, K.I., Jan, N. (2017). *Calendula officinalis* – an important medicinal plant with potential biological properties. Proc. Indian Natl. Sci. Acad., 83(4), 769–787. DOI: 10.16943/ptinsa/2017/49126

Kaur, J., Sidhu, S., Chopra, K., Khan, M.U. (2016). *Calendula officinalis* ameliorates l-arginine-induced acute necrotizing pancreatitis in rats. Pharm. Biol., 54(12), 2951–2959. DOI: 10.1080/13880209.2016.1195848

Khalid, K.A., Silva, J.A.T. (2012). Biology of *Calendula officinalis* Linn.: Focus on pharmacology, biological activities and agronomic practices. Med. Aromat. Plant Sci. Biotechnol. 6, 12–27.

Kurkin, V.A., Sharova, O.V. (2007). Flavonoids from *Calendula officinalis* flowers. Chem. Nat. Compd., 43(2), 216–217. DOI: 10.1007/s10600-007-0084-3

Leach, J.M. (2008). *Calendula officinalis* and wound healing: a systematic review. Wounds, 20(8), 236–243.

Legha, M.R., Prasad, K.V., Singh, S.K., Kaur, C., Arora, A., Kumar, S. (2012). Induction of carotenoid pigments in callus cultures of *Calendula officinalis* L. in response to nitrogen and sucrose levels. Vitr. Cell. Dev. Biol. – Plant, 48(1), 99–106. DOI: 10.1007/s11627-011-9402-3

Lima, M.R., Lopes, A.P., Martins, C., Brito, G.A.C., Carneiro, V.C., Goes, P. (2017). The effect of *Calendula officinalis* on oxidative stress and bone loss in experimental periodontitis. Front. Physiol., 8, 1–9. DOI: 10.3389/fphys.2017.00440

Lohani, A., Mishra, A.K., Verma, A. (2018). Cosmeceutical potential of geranium and calendula essential oil: Determination of antioxidant activity and *in vitro* sun protection factor. J. Cosmet. Dermatol., 1–8. DOI: 10.1111/jocd.12789

Lovecka, P., Lipov, J., Thumova, K., Macurkova, A. (2018). Characterization of biologically active substances from *Calendula officinalis*. Curr. Pharm. Biotechnol., 19, 1167–1174. DOI: 10.2174/1389201019666180226151910

Miguel, M., Barros, L., Pereira, C., Calhelha, R.C., Garcia, P.A., Castro, M.Á., Santos-Buelga, C., Ferreira, I.C.F.R. (2016). Chemical characterization and bioactive properties of two aromatic plants: *Calendula officinalis* L. (flowers) and *Mentha cervina* L. (leaves). Food Funct., 7(5), 2223–2232. DOI: 10.1039/c6fo00398b

Muley, B.P., Khadabadi, S.S., Banarase, N.B. (2009). Phytochemical constituents and pharmacological activities of *Calendula officinalis* Linn (*Asteraceae*): A review. Trop. J. Pharm. Res., 8(5), 455–465. DOI: 10.4314/tjpr.v8i5.48090

Neukirch, H., D'Ambrosio, M., Dalla Via, J., Guerriero, A. (2004). Simultaneous quantitative determination of eight triterpenoid monoesters from flowers of 10 varieties of *Calendula officinalis* L. and characterisation of a new triterpenoid monoester. Phytochem. Anal., 15(1), 30–35. DOI: 10.1002/pca.739

Nicolaus, C., Junghanns, S., Hartmann, A., Murillo, R., Ganzera, M., Merfort, I. (2017). *In vitro* studies to evaluate the wound healing properties of *Calendula officinalis* extracts. J. Ethnopharmacol., 196, 94–103. DOI: 10.1016/j.jep.2016.12.006.

Nizyński, B., Alsoufi, A.S.M., Pączkowski, C., Długosz, M., Szakiel, A. (2015). The content of free and esterified triterpenoids of the native marigold (*Calendula officinalis*) plant and its modifications in *in vitro* cultures. Phytochem. Lett., 11, 410–417. DOI: 10.1016/j.phytol.2014.12.017

Okoh, O.O., Sadimenko, A.A., Afolayan, A. (2007). The effects of age on the yield and composition of the essential oils of *Calendula officinalis*. J. Appl. Sci., 7(23), 3806–3810. DOI: 10.3923/jas.2007.3806.3810

Okuma, C.H., Andrade, T.A.M., Caetano, G.F., Finci, L.I., Maciel, N.R., Topan, J.F., Cefali, L.C., Polizello, A.C.M., Carlo, T., Rogerio, A.P., Spadaro, A.C.C., Isaac, V.L.B., Frade, M.A.C., Rocha-Filho, P.A. (2015). Development of lamellar gel phase emulsion containing marigold oil (*Calendula officinalis*) as a potential modern wound dressing. Eur. J. Pharm. Sci., 71, 62–72. DOI: 10.1016/j.ejps.2015.01.016

Parente, L.M.L., Souza Lino Jr, R. de, Tresvenzol, L.M.F., Vinaud, M.C., Paula, J.R. de, Paulo, N.M. (2012). Wound healing and anti-inflammatory effect in animal models of *Calendula officinalis* L. growing in Brazil. Evid.-Based Complement. Altern. Med., 2012, 1–7. DOI: 10.1155/2012/375671

Paul, S., Rahman, A., Mahmud, M., Uzzal, A., Das, Z. (2018). Wound healing by marigold (*Calendula officinalis*) and turmeric (*Curcuma longa*) Paste: a comparative approach. J. Adv. Vet. Anim. Res., 4(4), 333. DOI: 10.5455/javar.2017.d229

Pedram Rad, Z., Mokhtari, J., Abbasi, M. (2019). Preparation and characterization of *Calendula officinalis*-loaded PCL/gum arabic nanocomposite scaffolds for wound healing applications. Iran. Polym. J., 28(1), 51–63. DOI: 10.1007/s13726-018-0674-x

Pommier, P., Gomez, F., Sunyach, M.P., D'Hombres, A., Carrie, C., Montbarbon, X. (2004). Phase III randomised trial of *Calendula officinalis* compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. J. Clin. Oncol., 22(8), 1447–1453. DOI: 10.1200/JCO.2004.07.063

Preethi, K.C., Kuttan, R. (2009). Wound healing activity of flower extract of *Calendula officinalis.* J. Basic Clin. Physiol. Pharmacol., 20(1), 73–79. DOI: 10.1515/jbcpp.2009.20.1.73

Reider, N., Komericki, P., Hausen, B.M., Fritsch, P., Aberer, W. (2001). The seamy side of natural medicines: Contact sensitization to arnica (*Arnica montana* L.) and marigold (*Calendula officinalis* L.). Contact Dermatitis, 45(5), 269–272. DOI: 10.1034/j.1600-0536.2001.450503.x

Ruszkowski, D., Szakiel, A., Janiszowska, W. (2005). Metabolism of [3-3H]oleanolic acid in *Calendula officinalis* L. root. Acta Physiol. Plant., 25(4), 311–317. DOI: 10.1007/s11738-003-0011-6

Saffari, E., Mohammad-Alizadeh-Charandabi, S., Adibpour, M., Mirghafourvand, M., Javadzadeh, Y. (2017). Comparing the effects of *Calendula officinalis* and clotrimazole on vaginal *Candidiasis*: A randomized controlled trial. Women Heal., 57(10), 1145–1160. DOI: 10.1080/03630242.2016

Salehi, B., Anil Kumar, N.V., Şener, B., Sharifi-Rad, M., Kılıç, M., Mahady, G.B., Mehtap, K., Vlaicavljevic, S., Iriti, M., Kobarfard, F., Setzer, W.N., Ayatollahi, S.A., Ata, A., Sharifi-Rad, J. (2018). Medicinal plants used in the treatment of human immunodeficiency virus. Int. J. Mol. Sci., 19(5), 1459. DOI: 10.3390/ijms19051459

Samochowiec, E., Urbanska, L., Manka, W., Stolarska, E. (1979). Assessment of the action of *Calendula officinalis* and *Echinacea angustifolia* extracts on *Trichomonas vaginalis in vitro*. Wiad. Parazytol., 25(1), 77–81.

Shafeie, N., Naini, A.T., Jahromi, H.K. (2015). Comparison of different concentrations of *Calendula officinalis* gel on cutaneous wound healing. Biomed. Pharmacol. J., 8(2), 979–992. DOI: 10.13005/bpj/850

Shankar, S.M., Bardvalli, S.G., Jyotirmayee, R., Chethana, Bhushan, K., Kumar, S. (2017). Efficacy of *Calendula officinalis* extract (marigold flower) as an antimicrobial agent against oral microbes: An *in vitro* study in comparison with chlorhexidine digluconate. J. Clin. Diagnostic Res., 11(10), ZC05-ZC10. DOI: 10.7860/JCDR/2017/29844.10702

Shivasharan, B.D., Nagakannan, P., Thippeswamy, B.S., Veerapur, V.P., Bansal, P., Unnikrishnan, M.K. (2013). Protective effect of *Calendula officinalis* Linn. flowers against 3-nitropropionic acid induced experimental Huntington's disease in rats. Drug Chem. Toxicol., 36(4), 466–473. DOI: 10.3109/01480545.2013.776583

Singh, M.K., Sahu, P., Nagori, K., Dewangan, D., Alexander, T.K.A., Badwaik, H., Tripathi, D.K. (2011). Organoleptic properties *in-vitro* and *in-vivo* pharmacological activities of *Calendula officinalis* Linn.: An over review. J. Chem. Pharm. Res., 3(4), 655–663.

Toropova, A.A., Badmaev, N.S., Razuvaeva, Y.G., Nikolaev, S.M., Sambueva, Z.G., Erentueva, A. (2017). Influence

of *Calendula officinalis* extract on the antioxidant and energy status of liver in rats with experimental hepatitis. Eksp. Klin. Farmakol., 80(7), 11–14.

Tundis, R., Loizzo, M.R., Bonesi, M., Menichini, F. (2015). Potential role of natural compounds against skin aging. Curr. Med. Chem., 22(12), 1515–1538. DOI: 10.2174/0929867322666150227151809

FDA – U.S. Food & Drug Administration. Available: https://www.fda.gov/ [data of access: 22.01.2019].

Ukiya, M., Akihisa, T., Yasukawa, K., Tokuda, H., Suzuki, T., Kimura, Y. (2006). Anti-inflammatory, anti-tumor-promoting, and cytotoxic activities of constituents of Marigold (*Calendula officinalis*) flowers. J. Nat. Prod., 69(12), 1692–1696. DOI: 10.1021/np068016b

WHO (2002). Monographs on selected medical plants, vol. 2. Geneva.

Wiktorowska, E., Długosz, M., Janiszowska, W. (2010). Significant enhancement of oleanolic and accumulation by biotic elicitors in cell suspension cultures of *Calendula officinalis* L. Enzyme Microb. Technol., 46, 14–20. DOI: 10.1016/j.enzmictec.2009.09.002

Xuan, S.H., Kim, G.Y., Yu, J.Y., Kim, J.W., Yang, Y.R., Jeon, Y.H., Jeong, Y.J., Kim, R.A., Park, S.N. (2016). Antioxidant and cellular protective effects against oxidative stress of *Calendula officinalis* flowers extracts in human skin cells. Appl. Chem. Eng., 27(6), 620–626. DOI: 10.14478/ace.2016.1093

Xuan, S.H., Park, Y.M., Park, S.N. (2019). Antimelanogenic and antimigration properties of the ethyl acetate fraction of *Calendula officinalis* flowers on melanoma cells. Photochem. Photobiol., 95(3), 860–866. DOI: 10.1111/php.13064