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Review paper

Salvia sclarea: CHEMICAL COMPOSITION AND BIOLOGICAL ACTIVITY

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ABSTRACT: Clary sage (*Salvia sclarea* L.) is native to Southern Europe and is cultivated worldwide, as ornamental, as well as essential oil bearing plant.Clary sage is well known for its high value essential oil, widely used in perfumery. Besides, the oil possesses high biological activity and because of that is used against stress, tension, depression, insomnia, etc. However, traditionally clary sage oil was used an agent against gingivitis, stomatitis and aphthae. Apart of that, recent studies reported analgesic, anti-inflamatory, antimicrobial, antidiabetic and cytotoxic effects. Studies on clary sage seed fatty oil show that it is a good source of edible oil rich in omega 3-linoleic acid. Clary sage is also used in alcoholic beverages, as well as in tobacco industry. Novel investigations indicated that clary sage have great potential in agriculture because of phytoremediation, allelopathic and insecticidal properties.

Key words: *clary sage, essential oil, fatty oil, aroma fixative*

INTRODUCTION

Clary sage (*Salvia sclarea* L.) is native to Southern Europe and is cultivated worldwide, as ornamental, industrial and essential oil bearing plant. It is distributed through the temperate and sub-tropical climate, especially in the Mediterranean region and Central Europe. Commercially, in large scale it is cultivated in Russia, Bulgaria, France and Morocco, with annual world production of about 150 t of essential oil (Džamić et al., 2008; Hristova et al., 2013; Yaseen et al., 2015). Clary sage is biennial or perennial plant, with thick, sqare, erect stem, 20-120 cm high, branched toward the top. Stem pubescent to hirsute, in the upper part covered by glandular, gray hairs that give the balsam fragrance. Annual leaves are in rosette, while biennial (and later) are arranged along the stem in pairs. Lower leaves are with petiole, 2-7 cm long; upper are ± sessile, ovate to obovate. Simple and multicellular glandular trichomes are present on both sides of leaves. The leaf margins are crenate-erose (Hedge, 1972; Diklić, 1974). The results showed that drought stress significantly affects both, plant height and leaf size (Asadi et al., 2012). In agroecological conditions of Serbia, flowering time of clary sage is from June to August. Bracts exceeding corolla, lilac or white. Flowers (2-6) are arranged in verticals, while inflorescence is up to 40 cm long paniculates. Flowers have zygomorphic symmetry, and set in the bract base. Pedicel is 2-4 mm length. The calyx with spinose teeth, pubescent and glandular-punctate, with tridentate and mucronate upper lip, and bidentate lower lip, 10 mm long. Calyx is covered by glandular and simple trichomes. Corolla is 2-3 time long as calyx, lilac to whitish, 20-30 mm long. The corolla tube is short. Upper lip falciform, bilobulare, lower lip broad, trilobulare. Filaments are 2 mm long, anthers purple. The style is purple, longer than corolla. The fruit is nutlet. Seeds are brown, rounded to triangular (Hedge, 1972; Diklić, 1974). However, from starting vegetation to flowering it pass 88-161 days to flowering and 154-206 days to maturity. On the basis on the maturity the accessions were classified as: early (less than 170 days), medium (170-200 days) and late (more than 200 days) (Yaseen et al., 2014; Yaseen et al., 2015). Clary sage is well known for its high value essential oil, widely used in perfumery industries as a source of fragrance with refreshing and long lasting note. Besides, the oil has also got several medicinal properties and used in stress, tension, depression, insomnia, etc. (Yaseen et al., 2014). Apart of that, there are data on traditional use of clary sage oil as an agent against gingivitis, stomatitis and aphthae (Kostić et al., 2017). However, recent studies reported analgesic, anti-inflamatory, antimicrobial and cytotoxic effects (Gulcin et al., 2004). Studies on clary sage seed fatty oil show that it is a good source of edible oil rich in omega 3-linoleic acid (Tulukcu et al., 2012; Taarit et al., 2012). The flowers, leaves and stems of the clary sage are widely been used for food application and herbal tea as antidirrhea and tranquillizer drug in Turkish folk medicine (Gulcin et al., 2004; Tulukcu et al., 2012).

Clary sage have good potential to grow in Serbia, therefore, the main objective of the present study was to review the chemical composition and biological activity of this plant, and to promote their usage in everyday life.

CLARY SAGE ESSENTIAL OIL

Clary sage essential oil is obtained from fresh spikes of clary sage in full flowering stage. These contain individual flowers, their peduncles, bracts and varying quantities of leaves located above the basal rosette and attached to the main inflorescence stem (Caissard et al., 2012). Essential oil content ranged from 0.01 to 0.40% (Kuzma et al., 2009; Verma, 2010; Dogan et al., 2015). Clary sage oil is important commercial oil and characterized in the European Pharmacopoeia as a liquid that can be colorless, brownish-yellow or pale yellow, with characteristic odor. Relative density ranges from 0.890 to 0.908, refractive index ranges from 1.456 to 1.466, optical rotation is between -26° and -10°, and acid value is maximum 1.0 (PH. EUR. 7.0, 2010).

CHEMICAL COMPOSITION OF ESSENTIAL OIL

Notable differences in the linalool/linalyl acetate ratio among oil samples from different geographic regions were detected (Hristova et al., 2013). However, according to available literature (Table 1), linalyl acetate in clary sage essential oil ranges from 2.60% (Kuzma et al., 2009) to 56.88% (Hristova et al., 2013), while linalool content ranges from 8.50 (Dogan et al., 2015) to 40.24 (Verma, 2010). The linalyl acetate content characterizes the fragrance of clary sage oil – sweet, green, floral and spicy with a clean, woody, terry and citrus nuance (Szentmihalyi et al., 2009).

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Table 1. Chemical composition of different clary sage samples according to literature

COUNTRY		SERBIA	POLAND	IRAN	INDIA	TAJIKISTAN	INDIA	BULGARIA	GERMANY	TURKEY	GREECE	AVERAGE
LITERATURE SOURCE / COMPONENT	Ph. Eur. 7.0, 2010	Džamić et al., 2008	Kuzma et al., 2009	Saharkhiz et al., 2009	Verma, 2010	Sharopov and Setzer, 2012	Sharma and Kumar, 2012	Hristova et al., 2013	Sharopov et al., 2015	Dogan et al., 2015	Koutsaviti et al., 2016	
linalyl acetate	56-78	52.83	2.60	23.08	34.51	39.20	32.11	56.88	36.33	11.30	21.90	31.07
linalool	6.5-24	18.18	38.60	30.03	40.24	12.50	19.10	20.75	23.47	8.50	19.70	23.11
α-terpineol	max 5	5.00	14.30	11.13	5.17	5.50	7.15	2.64	8.12	4.50	6.80	7.03
geranyl acetate	-	-	5.80	8.37	3.03	3.50	6.68	1.22	2.30	-	4.40	3.53
sclareol	0.4-2.6	0.06	0.10	-	0.38	1.20	3.62	0.21	14.62	-	13.20	3.34
germacrene D	1-12	0.84	2.20	0.58	-	11.40	3.51	5.08	0.52	0.70	4.40	2.92
spathulenol	-	0.13	1.50	-	-	0.20	-	0.20	0.18	19.00	0.40	2.16
caryophyllene oxide	-	0.27	2.20	-	-	0.20	0.55	0.20	1.11	15.50	0.10	2.01
neryl acetate	-	0.52	3.00	4.69	1.26	1.90	3.27	0.71	1.05	-	2.30	1.87
trans-β-caryophyllene	-	1.83	1.10	-	3.15	2.40	2.20	3.41	0.62	1.80	0.70	1.72
β-myrcene	-	1.01	3.40	2.96	5.47	0.70	-	0.48	0.20	0.70	1.60	1.65
geraniol	-	-	7.70	-	1.76	-	-	-	0.31	-	2.30	1.21
nerol	-	0.26	2.50	2.54	0.40	1.10	-	0.44	0.76	0.70	1.50	1.02
α-eudesmol	-	-	0.30	-	-	0.80	2.61	-	1.22	2.20	0.70	0.78
limonene	-	1.55	0.90	-	1.76	0.20	-	0.20	0.66	-	0.50	0.58
manool	-	-	0.10	-	-	-	3.04	-	1.01	-	1.50	0.57
cis-β-ocimene	-	0.32	0.90	1.82	1.00	0.10	-	0.21	-	-	1.10	0.55
α- and β-thujone	max 0.2	-	-	-	-	0.90	-	-	-	-	-	0.09
TOTAL		83.35	88.40	85.20	98.13	82.80	83.84	93.50	92.76	64.90	83.70	

Linalool has an ecological role since it constitutes one of common components of floral scent that can attract a large variety of insects that convey pollen (Taarit et al., 2014). In addition to the commercial grade clary sage oil, other chemotypes have been identified, including a geraniol/geranyl acetate-rich chemotype from Israel, a methyl chavicol-rich chemotype from Sardinia, a germacrene D-rich chemotype from Sicily, and α-thujone, thujene and manool oxide/phytolchemotypes from Tunisia (Sharopov and Setzer, 2012). As it can be seen from Table 1, these 18 compounds constitute up to 80%, except in case clary sage samples from Turkey. In this case, other significant compounds were: 1H-naphtol[2,1-b]pyran (7.00%), lavandulyl acetate (3.80%), 1,5-epoxy salvial-4[14]-ene (2.00%), cadalene (1.60%), valeranone (1.50%), abietal (1.5%), lavandulylisobutanoate (1.50%), isospathulenol (1.2%), δ-selinene (1.10%) and salvialenone (1.00%), which represent 87.1% of all identified compounds (Dogan et al., 2015). Oxygenated monoterpenes were the major group representing 84.57% of the total oil composition, followed by sesquiterpenes 12.34%, monoterpenes 1.47%, oxygenated sesquiterpenes 0.61% and other compounds 1.02% (Hristova et al., 2013). Linalool (monoterpene alcohol) and linalyl acetate (monoterpene ester) levels seemed to decrease when duration of hydrodistillation increased, while diterpenes increased (Koutsaviti et al., 2016). However, a high concentration of alcohols (linalool, α-terpineol and geraniol) in the recovered oil and monoterpene and sesquiterpene hydrocarbons in the decanted oil has also been reported in case of rose, lavender and palmarosa. This is due to higher aquareus solubility of oxygenated compounds compared with terpene hydrocarbons (Verma, 2010). Apart from geographic origin and distillation technique, phenological stages as well as fertilization influence the quantity and quality of clary sage essential oil. The results of investigations on changes in essential oil content and composition of clary sage aerial parts during different phenological stages showed differences. It is strongly believed that these differences are due to variations in the metabolic pathways and consequently modifications in secondary metabolism which coupled with the plant growth and development (Saharkhiz et al., 2009). Further, fertilization with different rates of nitrogen (0, 1.5, 3.0, 4.5 and 6.0 g N/plant) show significant differences in chemical composition, where the dose of 3.0 g N/plant recorded significantly higher content of linalyl acetate and linalool (Sharma and Kumar, 2012). Sclareol is a high value natural product obtained from clary sage (Caissard et al., 2012). Sclareol possesses very little aroma but it is extremely useful in perfumery for its “fixing” power. This versatile diterpene alcohol is also the starting material for an important series of perfume and flavour chemicals (Leffingwell et al., 1974). However, sclareol is less volatile than monoterpenes and sesquiterpenes, and spontaneously crystallises at ambient temperature (Caissard et al., 2012). Hydrodistillation of full ripened seeds of clary sage offered 0.05% of essential oil, with linalool as dominant compound with 24.25%, followed by α-thujene (7.48%), linalyl acetate (6.90%) and germacrene D (5.88%). Other significant compounds are: bicyclogermacrene, α-copaene, caryophyllene oxide, α-cubebene, geraniol, geranylacetate, carvacrol, β-eudesmol, humulene epoxide I, cis-alo-ocimene and germacrene B (Taarit et al., 2014).

CLARY SAGE FATTY OIL

Clary sage seeds are rich in fatty acids and contained high levels of antioxidant and antiradical activities making them ideal for use as nutraceuticals. Oil content in clary sage seed ranged from 23.83% to 29.34%. Polyunsaturated fatty acids were the most abundant fatty acid in the clary sage seed. The content of α-linoleic acid varied between 50.04 and 53.69%, followed by oleic (20.10-22.97%) and linoleic acid (15.54-18.06%).

Saturated fatty acids (palmitic and stearic) are present in low percent (in average 6.65% and 2.44%, respectively) (Tulukcu et al., 2012), the reason of which clary sage has become a source of popular edible safe oil (Taarit et al., 2012). Clary sage represents one of the known vegetable sources for omega 3-linoleic acid to the functional food industry. Polyunsaturated fatty acids fraction (59.57%) is the prevailing one represented by α-linoleic (C18:3n-3) and linoleic (C18:2n-6) acids. However, clary sage is one new crop with constitutes a source of α-linoleic acid. Like highly recommended edible crops, clary sage leaves is characterised by a reduced saturated fatty acid proportion, and low n-6:n-3 ratio and therefore have an appreciable dietary nutraceuticals value (Taarit et al., 2012). In average, the content of volatile compounds in the clary sage seeds from Turkeyis: 1-tridecene (5.82%), 2-ethyl-1-hexanol (4.89%), n-pentadecanol (4.37%), hexanal (3.11%), metoxy-phenyl-oxime (2.55%), isovaleric acid (2.53%), phenol (2.41%), tridecane, hexadecane, 2-E-dodecenal (2.28%), followed by lauryl alcohol, n-nonanol, α-terpineol, n-decanol, nonanal, tetradecane, naphthalene, linalool, n-hexadecanol, dihydrocitronellol acetate, 1-decene andoctadecene (Tulukcu et al., 2012). Apart from fatty oil, clary sage seed is rich in proteins, whose content varied from 20.42% to 22.96% (Tulukcu et al., 2012).

PHENOLIC COMPOUNDS AND ANTIOXIDATIVE ACTIVITY

Total phenolic content of different clary sage extract (water, ethanol and methanol) was in range from 63.9 to 134.4 mg GAE/g of plant. The highest antiradical activity was displayed by the methanol fractions of clary sage varieties from Ukraine (C 785 and Aj-Todor) 83 and 67%, respectively. HPLC-DAD analysis of extracts was done in order to identify the presence of individual phenolic compounds. Phenolic acids and flavonoids are well-known from their antioxidant properties, with derivatives of benzoic acid and hydroxycinnamates showing their antioxidant activities by hydrogen-donating mechanism (Jasicka-Misiak et al., 2018). Leaf methanolic extract of clary sage offered a total polyphenol content estimated for 24.4 mg GAE/g DW. Free radical scavenging capacities of the leaf extract measured through DPPH assay in average is58.20 μg/mL. From the other side, ability to prevent bleaching of β-carotene is 134.20 μg/mL (Taarit et al., 2012). The total phenolic content varied from 7.71 to 13.21 mg GAE/g dry extract, while antioxidant activity ranged between 50.45 and 74.04 mg AAE/g dry extract, and antiradical activity of the clary sage seed samples varied between 13.14 and 21.21% (Tulukcu et al., 2012). The chloroform extract of clary sage had stronger total antioxidant activity than the acetone extract and exhibited 93 and 68% inhibition of linoleic acid peroxidation, respectively. α-Tocopherol, quercetin, butylatedhydroxyanisole and butylatedhydroxytoluene were used as standard antioxidants (Gulcin et al., 2004).

ANTIMICROBIAL ACTIVITY

Clary sage essential oil demonstrated antifungal activity against clinical isolates of strains belongs to five different of genus *Candida* – *C. albicans* (MIC 210 μg/ml, MFC 402 μg/ml), *C. tropicalis* (MIC 768 μg/ml, MFC 768 μg/ml), *C. krusei* (224 μg/ml, MFC 448 μg/ml), *C. glabrata* (MIC 896 μg/ml, MFC 1024 μg/ml) and *C. parapsilosis* (MIC 256 μg/ml, MFC 384 μg/ml) (Hristova et al., 2013). Food poisoning agents, spoilage fungi and plant and animal pathogens were among the tested fungal species. A concentration of 25 µl/ml of clary sage oil showed fungicidal activity against *Aspergillus*, *Penicilium* and *Fusarium* species and *Trichoderma viridae*. For the species *Mucor mucedo* and *Aspergillus viridae* the MFC was 15 µl/ml, for *Candida albicans* it was 10 µl/ml. Fungistatic and fungicidal activities of the oil against *Cladosporium cladosporoides* and *Trichophyton menthagrophytes* were recorded at concentrations of 2.5 µl/ml and 5 µl/ml. The most sensitive micromycetes were *Cladosporium fulvum*, *Alternaria alternata*, *Phomopsis helianthi* and *Phoma macdonaldii* where a concentration of 2.5 µl/ml was lethal (Džamić et al., 2008). Among the bacteria tested (*Staphylococcus aureus*, *S. epidermis*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *C. albicans*), *E. coli* strain was the most sensitive microorganism to clary sage essential oil. However, the significant activity was also noted against *S. aureus* and *S. epidermis* strains (MIC values was 10.0 and 5.0 mg/mL, respectively) (Kuzma et al., 2009). Antimicrobial activities of both clary sage extracts (chloroform and acetone) were examined by means of disk-diffusion methods with 11 microbial species (*Bacillus megaterium*, *Proteus vulgaris*, *Listeria monocytogenes*, *Bacillus cereus*, *Staphylococcus aureus*, *Bacillus brevis*, *Klebsiella pneumoniae*, *Micrococcus luteus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Mycobacterium smegmatis*) and 4 fungal species (*Penicillum frequentans*, *Fusarium equiseti*, *Aspergillus candidus* and *Byssochlamys fulves*). Both clary sage extracts were effective in inhibiting the growth of the organisms except for *Escherichia coli*. The antifungal activity of each of the above extracts is lower than the antimicrobial activity (Gulcin et al., 2004).

CITOTOXIC ACTIVITY

Clary sage oil exhibited cytotoxic activity against acute lymphoblastic leukemia NALM-6 and promyelocytic leukemia HL-60 cell lines, whereas IC50 was 8.1-20.1 µg/mL, and 6.4-6.5 µg/mL, respectively (Kuzma et al., 2009). Clary sage cell and hairy root extracts the presence of different class of diterpenes, as well as novel compounds, which showed anti-tumoral activity against the epidermoid carcinoma cell line A431 (Felice et al., 2004).

ANTI-INFLAMATORY ACTIVITY

The clary sage oil showed a significant anti-inflammatory effect and moderate analgesic action after subcutaneous injection at a dose of 250 mg/kg. The anti-inflammatory action was more conspicuous in the carrageenin-induced edema, where it produced the equivalent effect of a 5 mg/kg dose of indomethacin, than in the histamine-induced edema. The effect was correlated to the presence of methyl chavicol, linalool, α-terpineol and linalyl acetate. The results show that these constituents produce less anti-inflammatory action when administered separately than the oil *in toto*, and are also less effective than the oxygenated fractions obtained by Flash chromatography of the oil. This indicates that the action of the oil is determined by synergistic action of its constituents. The moderate peripheral analgesia (evaluated by writhing test) produced by clary sage oil appears to be mainly attributable to its alcoholic component (Moretti et al., 1996). Clary sage extract manifested anti-inflammatory effect in lipopolysaccharide induced periodontitis suggesting that it may have a role as a therapeutic agent in periodontal diseases. Having in mind that overproduction of reactive oxygen species is connected to periodontitis, the strong antioxidant capacity may be contributable to anti-inflammatory properties of the extract (Kostić et al., 2017).

ANTI-ANXIETY ACTIVITY

Clary sage oil-treated submissive animals showed a significant reduction in blood corticosterone levels. These findings enforce the hypothesis that clary sage oil possesses anxiolytic properties (Gross et al., 2013). Clary sage oil had the strongest anti-stressor effect in the forced swim test. The mechanism of clary oil antidepression by pretreatment with agonists or antagonists to serotonin, dopamine, adrenaline and GABA receptors. The anti-stressor effect of clary oil was significantly blocked by pretreatment with buspirone, SCH-23390 and haloperidol, and receptor antagonist. Our findings indicate that clary oil could be developed as a therapeutic agent for patients with depression and that the antidepressant-like effect of clary oil is closely associated with modulation of the DAnergic pathway (Seol et al., 2010). Clary sage treatment of rats subjected to immobilization stress contributed to their recovery from endothelial dysfunction by increasing nitric oxide (NO) production and endothelial NO synthase (eNOS) level, as well as by decreasing oxidative stress. Appropriate concentration of clary sage may result in recovery from endothelial dysfunction. These findings indicate that clary sage oil may be effective in the prevention and treatment of stress-induced cardiovascular diseases (Yang et al., 2014).

ANTI-DIABETIC ACTIVITY

The acute and subchronicantidiabetic activities of clary sage essential oil have been monitored along with high linalool (average 40.2%) and high linalyl acetate concentrations (average 50.4%), in order to find the most active chemotype. Chemotype 1 (high linalool content), present at low altitude places of Lebanon and Poland, has shown significantly higher acute and subchronic antidiabetic activities than that of chemotype 5 (high linalyl acetate content). In conclusion, clary sage essential oil have shown potential antidiabetic activity, and it might be used in the future as a complementary or an alternative medicine in the management of diabetes and related complications (Raafat and Habib, 2018).

AROMATHERAPY USE

In aromatherapy, clary sage is used as an effective relaxant for the treatment of stress, asthma, digestive and menstrual problems and in addition (Verma, 2010). Clary oil inhalation may be useful in inducing relaxation in female urinary incontinence patients undergoing urodynamic assessments (Seol et al., 2013). It is most frequently applied in aromatization of candles for deodorization and against depression and stress. Its effect is affirmed with juniper, lemon, geranium, jasmine and spike oil (Szentmihalyi et al., 2009).

PARFUMERY

Clary sage essential oil is widely employed in perfumery where it is greatly appreciated for both odorous qualities and as an excellent fixer. In addition, sclareol is a principal bioactive compound that may be also used to produce Ambrox, a chemical compound in the class of tetralabdanoxides considered as one of the most valuable perfumes of animal origin. Previously, the source of Ambrox was Ambra, a waxy substance from the digestive tract of the whale (Gonceariuc et al., 2016).

FOOD INDUSTRY

The clary sage essential oil is used in food industry to produce beer, tonic beverages, liquers, as well as Muscat and Vermouth type wines (Gonceariuc et al., 2016).

TOBACO INDUSTRY

As for aroma of Oriental tobacco, one of the most important contributors to the amber/tobacco-like dry out note is undoubtedly clary sage (Leffingwell et al., 1974).

PHYTOREMEDIATION

Clary sage is a plant which is tolerant to heavy metals and can be grown on contaminated soils. Clary sage can be classified as Pb hyperaccumulator and accumulator of Cd and Zn, therefore, this plant has suitable potential for the phytoremediation of heavy metal contaminated soils. Favourable is also the fact that heavy metals do not influence the development of the clary sage as well as on the quality and quantity of the essential oil. The possibility of further industrial processing will make clary sage an economically interesting crop for farmers of phytoextraction technology (Angelova et al., 2016).

ALLELOPATHY

Allelopathy is an interference mechanism in which plants release chemical substances, called allelochemicals which inhibit or stimulate plant growth. Accordingly, allelopathy is a natural and an environment-friendly technique which may prove to be also a unique tool for weed control. Clary sage aqueous extract on the activity of the antioxidant enzymes in leaves and roots of bromus (*Bromus mollis* L.), black nightshade (*Solanum nigrum* L.) and Jimson weed (*Datura stramonium*) seedlings. These results indicated that the clary sage as source of natural substances is good candidates in developing natural pesticides (Šućur et al., 2015; Šućur et al., 2016a; Šućur et al., 2016b).

INSECTICIDAL ACTIVITY

Secondary metabolites from plant also have a role in plant – insect interaction. It was observed that clary sage aqueous extract showed toxic effect against lesser grain borer (*Rhyzopertha dominicana*) with high mortality rate (above 95%) and whitefly

(*Trialeurodes vaporariorum*) with 56.66% mortality (Šućur et al., 2015; Šućur et al., 2016b).

CONCLUSIONS

Clary sage is promising essential oil bearing plant, as well as oilseed crop. Essential oil of this plant is important fragrance in perfumery, tobacco and food industry. Clary sage fatty oil is a good source of edible oil rich in omega 3-linoleic acid. Novel investigations indicated that clary sage have great potential in agriculture because of phytoremediation, allelopathic and insecticidal properties.

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