International Journal of Biological and Pharmaceutical Sciences Archive

ISSN: 0799-6616 (Online)

Journal homepage: https://ijbpsa.com/

(REVIEW ARTICLE)

Pharmacological and toxicological effects of the *Ranunculus* species (*Ranunculus arvensis* and *Ranunculus sceleratus*) grown in Iraq

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International Journal of Biological and Pharmaceutical Sciences Archive, 2022, 03(01), 064–072

Publication history: Received on 21 January 2022; revised on 07 March 2022; accepted on 09 March 2022

Article DOI: https://doi.org/10.53771/ijbpsa.2022.3.1.0032

Abstract

The current review revealed that *Ranunculus arvensis* contained carbohydrates, protein, amino acids, tannins, glycosides, phenols steroids, sterols, saponosides, leucoanthocyanes, di and tri terpenes, coumarins and flavanoids. It possessed antimicrobial, antioxidant and antitumor effects. *Ranunculus sceleratus* contained amino acid, proteins, alkaloids, phytosterols, flavonoids, steroids, fatty acid, terpenoids, phenols, saponin, tannins and resins. It exerted antibacterial, antifungal, antiviral, antiparasitic, antioxidant and anti-inflammatory effects. However both species were not free from adverse effects.

Keywords: *Ranunculus arvensis*; *Ranunculus sceleratus*; Pharmacology; Constituents; Toxicity

1. Introduction

As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. Two thirds of the new chemicals identified yearly were extracted from higher plants. 75% of the world's population used plants for therapy and prevention. In the US, where chemical synthesis dominates the pharmaceutical industry, 25% of the pharmaceuticals are based on plant-derived chemicals**.** Medicinal plants contained many biologically active ingredients which possessed wide range of pharmacological effects[1-13]. *Ranunculus arvensis* contained carbohydrates, protein, amino acids, tannins, glycosides, phenols steroids, sterols, saponosides, leucoanthocyanes, di and tri terpenes, coumarins and flavanoids. It possessed antimicrobial, antioxidant and antitumor effects. *Ranunculus sceleratus* contained amino acid, proteins, alkaloids, phytosterols, flavonoids, steroids, fatty acid, terpenoids, phenols, saponin, tannins and resins. It exerted antibacterial, antifungal, antiviral, antiparasitic, antioxidant and anti-inflammatory effects. However, both contained ranunculin which hydrolyzed into protoanemonin upon crushing of plant tissue. Protoanemonin is an irritant to skin, eyes and mucosal surface; it binds sulphydryl groups and disrupts disulphide bonds, leading to disruption of skin architecture and formation of bulla. Contact with protoanemonin causes dermatitis, burning and itching with accompanying rash and blisters. If the leaves are chewed by humans or beasts, blisters may form on the lips and face. The toxic oil is also a serious eye irritant. In swallowing of some buttercups, patient will complain abdominal pain, diarrhea, vomiting, dizziness and even paralysis. The current review discuss the constituents, pharmacological and toxicological effects of *Ranunculus arvensis*and *Ranunculus sceleratus*.

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2. Plants profiles

2.1. Ranunculus arvensis

2.1.1. Synonyms

Cynomorbium heterophyllum, *Hericinia arvensis*, *Pfundia arvensis*, *Ranunculus arvensis* var. *tuberculatus*[14].

2.1.2. Taxonomic classification

Kingdom: Plantae, Subkingdom: Viridiplantae, Infrakingdom: Streptophyta, Superdivision: Embryophyta, Division: Tracheophyta, Subdivision: Spermatophytina, Class: Magnoliopsida, Superorder: Ranunculanae, Order: Ranunculales, Family: Ranunculaceae, Genus: Ranunculus, Species: *Ranunculus arvensis*[15].

2.1.3. Common names

Arabic: KaffAlhirr; English: corn buttercup, corn crowfoot, field buttercup; French: renoncule des champs, Swedish: åkerranunkel[16].

2.1.4. Distribution

It is distributed in Africa (Algeria, Egypt, Morocco, Tunisia), Asia (Iran, Iraq, Palestine, Lebanon, Syria, Turkey, Russian Federation- Ciscaucasia, Armenia, Azerbaijan, Georgia, Tajikistan, Turkmenistan, Uzbekistan, India, Pakistan) and Europe (United Kingdom, Sweden, Austria, Belgium, Switzerland, Czech Republic, Hungary, Netherlands, Poland, Slovakia, Ukraine, Albania, Bulgaria, Bosnia and Herzegovina, Greece, Croatia, Italy, North Macedonia, Montenegro, Romania, Serbia, Slovenia, Spain, France, Portugal)(16).

2.1.5. Description

Annual, 10-50 cm high, branched, sparsely hairy especially above. Lower most leaves with a distinct petiole equalling or slightly longer than the leaf-blade, blade obovate-spathulate to oblanceolate, cuneate at apex, apex incised or with a few irregular teeth. Other leaves 3-parted to ternate with obovate-spathulate segments again deeply divided into linear, toothed or entire lobes (2-6 mm wide). Flowers 5-12 mm in diameter, sulphur yellow to greenish-yellow. Sepals patent, with long hairs outside. Petals obovate, indistinctly clawed. Achenes inserted in the pubescent receptacle, 4-8 in a single whorl, 4-6 mm long, obovate, strongly compressed with a broad sulcate border, spiny or tuberculate[17].

2.1.6. Traditional uses

It was used traditionally in the treatment of asthma, rheumatism, high fever, gut disease[5]. It was also used for abscess drainage, blister formation, hemorrhoids, and as herbal remedies for myalgia and common cold[19-22]. The plant is known to be a poison when it is fresh[18].

2.1.7. Chemical constituents

The preliminary phytochemical analysis of*Ranunculus arvensis* revealed the presence of carbohydrates, protein, amino acids, tannins, glycosides, phenols steroids, sterols, saponosides, leucoanthocyanes, di and tri terpenes, coumarins and flavanoids[23].

Ranunculus arvensis gave (0.12%) essential oil, (1280 **±** 50 mg/kg) Fe and (15 **±**0.49 mg/kg) Cu. The main compounds in the oil were guaiol (8.81%), caryophyllene oxide (7.1%), spathulenol (6.73%) and camphor (6.2%)[24].

The total content of flavonoid in the chloroform: methanol extract of *Ranunculus arvensis* was 1.95 ± 0.01, in methanol extract 6.00 ± 0.02, in methanol: acetone extract 1.08 ± 0.01, in acetone extract 0.96 ± 0.01, in methanol: water extract 5.72 ± 0.01 and in water extract 2.19 ± 0.01 mg RE/g dry extract. The total phenol content in the methanol extract was 0.48 ± 0.03, in methanol: water extract was 1.06 ± 0.02 and in water extract was 1.43 ± 0.01 GAE/g dry extract. Chemical analysis of the methanol extract of *Ranunculus arvensis* showed the presence of rutin (0.44%) and caffeic acids (0.017%). Smaller amount of rutin (0.01%) was detected in the methanol: water extract and small amount of caffeic acid (0.008%) was detected in the water extract[25]. Quercetin, isovitexin and isoorientin were also identified in *Ranunculus arvensis*[26].

2.1.8. Pharmacological effects

Antimicrobial effect

The antibacterial activity of methanol, water, acetone, chloroform, methanol-water, methanol-acetone, methanol-chloroform extracts of *Ranunculus arvensis* was investigated against *Escherichia coli, Enterobacter aerogenes, Bordetella bronchiseptica, Klebsiella pneumoniae, Micrococcus luteus* and *Streptococcus anginosus*, while their antifungal activity was investigated against *Aspergillus niger, A. flavus, A. fumigates, Fusarium solani* and *Mucor* species. Water extract revealed weak antimicrobial result against the tested microorganisms. On the other hand, the antifungal activity of the plant extracts was found to be insignificant[27].

The antifungal effect of the aqueous extract of *Ranunculus arvensis* was investigated against *Candidasalbicans, Aspergillus niger, A clavatus* and *Penicillium digitatum.* The extract possessed potent antifungal activity with zones of growth inhibition of 14-21mm. *Candida albicans* showed the highest sensitivity to the extract (zones of growth inhibition: 21mm)[23].

Antioxidant effect

Ranunculus arvensis exhibited significant free radical scavenging potential. IC_{50} values in the DPPH, hydrogen peroxide scavenging and phosphor-molybdenum assays (µg/ml respectively) for chloroform extract were 330.29 ± 0.01, 124.36 ± 0.01 and 52.58 ± 0.01, for chloroform: methanol extract 186.28 ± 0.01, 101.6 ± 0.01 and 69.39 ± 0.03, for methanol extract 34.71 ± 0.02, 65.73 ± 0.01 and 66.06 ± 0.01, for methanol: acetone extract 285.28 ± 0.01, 134.68 ± 0.01 and 63.09 ± 0.01, for acetone extract 264.08 ± 0.01, 69.55 ± 0.01 and 56.29 ± 0.01, for methanol: water extract 47.61 ± 0.02, 43.53 ± 0.02 and 77.95 ± 0.01, and for water extract 85.11 ± 0.02, 51.27 ± 0.01 and 74.37 ± 0.01, while that of ascorbic acid were 6.38 ± 0.01, 39.05 ± 0.01 and 26.16 ± 0.01 µg/ml[25].

Antitumor and cytotoxic effects

Antitumor activity of methanol, water, acetone, chloroform, methanol-water, methanol-acetone, methanol-chloroform extracts of *Ranunculus arvensis* was evaluated with *Agrobacterium tumefaciens* (At10) induced potato disc assay. Cytotoxicity was evaluated with brine shrimp lethality assay. Best antitumor activity was obtained with methanol and water extracts, showing highest IC_{50} values 20.27 ± 1.62 and 93.01 ± 1.33µg/disc. Brine shrimp lethality assay showed LC_{50} values of acetone extract, methanol-acetone extract and methanol extract were obtained as 384.66 ± 9.42µg/ml, 724.11 ± 8.01µg/ml and 978.7 ±8.01 µg/ml respectively[27].

2.1.9. Toxicity

Skin burn (vesiculo-bullous lesions and swelling, second degree burn) associated with *Ranunculus arvensis* were recorded. Protoanemonins are volatile and highly irritating lipids that increase free oxygen radicals by inhibiting DNA polymerase. When they are applied on the skin they inflame the skin and damage the mucosal membranes in subcutis, produce blistering by demolishing the sulphide chains, lead to bulla formation and subepidermal separation. Protoanemonins are rapidly polymerized to anemonine that (they crystallized forms are harmless) are caustic poison containing two lactones. The withered or the boiled plants do not contain protoanemonins[28-33].

2.2. Ranunculus sceleratus

2.2.1. Synonyms

Adonis palustris, Batrachium sceleratum, Hecatonia palustris, Hecatonia scelerata, Ranunculus holophyllus, Ranunculus indicus, Ranunculus oryzetorum, Ranunculus sceleratus var. sceleratus, Ranunculus sceleratus f. sceleratus, Ranunculus sceleratus var. sinensis[34].

2.2.2. Taxonomic classification

Kingdom: Plantae, Subkingdom: Viridiplantae, Infrakingdom: Streptophyta, Superdivision: Embryophyta, Division: Tracheophyta, Subdivision: Spermatophytina, Class: Magnoliopsida, Superorder: Ranunculanae, Order: Ranunculales, Family: Ranunculaceae, Genus: Ranunculus, Species:*Ranunculus sceleratus*[35].

2.2.3. Common names

Arabic: Zaghlil, English: blister buttercup, celery buttercup, celery-leaf buttercup, celery-leaf crowfoot, cursed crowfoot, marsh crowfoot, poison buttercup; French: renoncule scélérate, Swedish: tiggarranunkel[36].

2.2.4. Distribution

It is distributed in Africa (Algeria, Egypt, Morocco, Tunisia), Asia (Afghanistan, Iran, Iraq, Palestine, Lebanon, Syria, Turkey, Russian Federation, Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, Mongolia, China, Japan, Bhutan, India, Nepal, Pakistan), Europe (Denmark, Finland, United Kingdom, Ireland, Norway, Sweden, Austria, Belgium, Switzerland, Czech Republic, Germany, Hungary, Netherlands, Poland, Slovakia, Russian Federation-European part, Belarus, Estonia, Lithuania, Latvia, Ukraine, Albania, Bulgaria, Bosnia and Herzegovina, Greece, Croatia, Italy, North Macedonia, Romania, Serbia, Slovenia, Spain, France, Portugal), and Northern America (Canada, USA)[36].

2.2.5. Description

Herbs annual. Roots fibrous, subequally thick. Stems 10-75 cm, glabrous or sparsely puberulent, branched above. Basal leaves 5-13; petiole 1.2-15 cm, subglabrous or sparsely pubescent; blade 3-partite, pentagonal, reniform, or broadly ovate, or broadly ovate, 1-4 × 1.5-5 cm, papery or herbaceous, glabrous or abaxially puberulent, base broadly cordate, central lobe cuneate or rhombic, 3-lobed, lobules 1- or 2-denticulate or entire; lateral lobes obliquely broadly obovate or obliquely cuneate, unequally 2-lobed or 2-cleft to middle. Lower stem leaves similar to basal ones; upper stem leaves short petiolate, cuneate at base, 3-sect, segments oblanceolate. Compound monochasi um terminal, corymbose; bracts leaflike. Flowers 0.4-0.8 cm in diam. Pedicel 0.5-1.5 cm, glabrous or sparsely puberulent. Reeptaclepuberulent or glabrous. Sepals 5, ovate-elliptic, 2-3 mm, abaxially appressed puberulent or glabrous. Petals 5, obovate, 2.2-4.5 × 1.4-2.4 mm, nectary pit without a scale, apex rounded. Stamens 10-19; anthers ellipsoid. Aggregate fruit cylindric, 3-11 × 1.5-4 mm; carpels numerous. Achene slightly bilaterally compressed, obliquely obovoid, 1-1.1 × 0.8-1 mm, glabrous, sometimes transversely 2- or 3-rugose, somewhat turgid along sutures; stigmas persistent[37].

2.2.6. Traditional uses

It was used traditionally as antiphlogostic, anti-diarrheal, as mastitis remedy and to relief articular effusion[38-39]. The plant was also used in the treatment of plague, malaria, scorpion bite, blood stasis, acute icteric hepatitis and internal abscess[40].

The plant was considered stimulant and diuretic. The leaves juice was used in sciatica, rheumatism, dysuria, asthma and pneumonia. Seeds were used to cure kidney troubles[41-42].

2.2.7. Part used medicinally

Whole plant, leaves, and seeds[40-43].

2.2.8. Chemical constituents

The preliminary phytochemical analysis of *Ranunculus sceleratus* showed that it contained amino acid, proteins, alkaloids, phytosterols, flavonoids, steroids, fatty acid, terpenoids, phenols, saponin, tannins and resins[40, 44].

Tannins amounts in the shoot and root extracts of *Ranunculus sceleratus* were 12.06±0.63 and 8.63±0.45, mg/g dried weight, saponins 16.87±0.89 and 15.98±0.84 mg/g dried weight, flavonoids 9.96±0.68 and 6.87±0.36 mg/g dried weight, alkaloids 3.88±0.20 and 2.57±0.14 mg/g dried weight and total Phenol 27.54±1.45 and 15.33±0.81 mg/g dried weight[45].

Ranunculus sceleratus, ethanol extract contained polyphenols 7.22±.02 mg gallic acid E/g, flavonoids 8.06±.07 mg quercetin E/g, and alkaloids 0.09±.007 mg atropine E/g. While the methanol extract contained polyphenols 0.9±.02 mg GAE/g, flavanoids 3.66±0.2 mg QE/g, and alkaloids 0.01±0.002 mg AE/g[46].

The total phenolic content of *Ranunculus sceleratus* hydroalcoholic extract was 0.03 and in glycerol-ethanol extract was 1.01 % mg/ml, while the total flavonoid content in hydroalcoholic extract was 10.16 and in glycerol-ethanol extract was 3.45 % mg/ml[39].

5-hydroxy tryptamine, apigenin, apigenin 7-O-β-glucopyranosyl-4′-O-α-rhamnopyranoside, apigenin 4′-O-α-rhamnopyranoside, tricin, tricin 7-O-β-glucopyranoside, anemonin, protoanemonin, ranunculin, scoparone, isoscopoletin, protocatechuic acid, protocatechuic aldehyde, stigmasta-4-ene-3,6-dione and stigmasterol were also isolated from *Ranunculus sceleratus*[38, 47-51].

Carboxylic acid, alcohol, alkene, amine, sulfone, aromatic amine, alkyl aryl ether, fluoro compound, halo compound in addition to phenolic compounds and flavonoids were also identified in *Ranunculus sceleratus*[40].

Amino acids (cystine, lysine, histidine, serine, methionine, proline and glutamic acid % respectively) in the aerial part were 19.60, 18.14, 9.29, 2.10, 8.14, 3.46, 2.45; in root: 24.12, 17.40, 9.04, 8.71, 7.53, 3.18 and 0%. While the amino acids in the seed (cystine, lysine, histidine, serine, methionine, threonine and tyrosine % respectively) were 12.85, 5.48, 1.70, 14.91, 22.08, 2.64, and 4.91. The sucrose, glucose and fructose in the aerial parts were 19.97, 19.75 and 52.05% and in the root 67.46, 4.76 and 27.77% respectively. Protoanemonin and anemonin were extracted from *Ranunculus sceleratus* [38].

2.2.9. Pharmacological effects

Antibacterial and antifungal effects

The antimicrobial effect of *Ranunculus sceleratus* root extracts was investigated against *Bacillus subtilis*, *Staphylococcus aureus, Acinetobacter baumannii, Pseudomons aeruginosa, Asperigillus niger* and *Saccharomyces cerevisiae*. Ethanol extract of *Ranunculus sceleratus* showed optimum inhibition activity, compared with methanol extract. MIC of the ethanolic extract was ranged from 21 to 17.67 mg/ml, and that of methanolic extract was ranged from 13.67 to 14 mg/ml against all the tested bacteria and fungi[52].

Studies of the antifungal effects of the leaf extract of *Ranunculus sceleratus* showed that it possessed quick fungicidal action, and broad fungicidal spectrum. The extract was lethal at 1:40 dilution and its volatile vapours were also fungitoxic[53-54].

The antifungal activity of *Ranunculus sceleratus* extracts was investigated against *T. rubrum* (MTCC 8477), *T. mentagrophytes* (MTCC 8476), *T. tonsurans* (MTCC 8475), *M. gypseum* (MTCC 8469) and *M. fulvum*. The growth inhibition zone of the chloroform extract was ranged from 15 to 23 mm (MIC 1.25-205mg/ml), and the growth inhibition zone of the methanol extract was ranged from 10 to 21 mm (MIC 20.5-5 mg/ml) against all the tested fungi, while the water extract showed antifungal activity against only *T. mentagrophytes* (8mm), *M. gypseum* (9mm) and *M. fulvum* (8mm) (MIC >10.0 mg/ml)[43].

Antiviral effect

Compounds isolated from *Ranunculus sceleratus* were tested for inhibitory effects on hepatitis B virus (HBV) and Herpes simplex virus type-1 (HSV-1). The results showed that apigenin 4'- O- alpha-rhamnopyranoside, apigenin 7- O- beta-glucopyranosyl-4'- O- alpha-rhamnopyranoside, tricin 7- O- beta-glucopyranoside, tricin, and isoscopoletin possessed inhibitory activity against HBV replication. Protocatechuyl aldehyde exhibited an inhibiting activity on HSV-1 replication[55].

Antiparasitic effect

In screening of 18 plant species to determine their inhibitory effects on *T. cruzi*. Methanol extracts of the aerial part of *Ranunculus sceleratus* and the root of *Coptis deltoidea* at a concentration of 250 μg/ml had significant inhibitory effects on *T. cruzi*. The inhibitory rates were 97 and 100%, respectively. If both extracts were mixed, the suppression rate of *T. cruzi* was very significant[56].

*Ranunculus sceleratus*is very effective as an insecticide against *Drosophila melanogaster* and *Tribolium castaneum*[57].

Antioxidant effect

The antioxidant activity of *Ranunculus sceleratus* extracts was investigated using 5 methods: DPPH, FRAP (ferric reducing ability of plasma), TEAC (trolox equivalent antioxidant capacity), CUPRAC (cupric reducing antioxidant capacity) and SNP (silver nanoparticle assay). IC_{50} values of the antioxidant activity of *Ranunculus sceleratus* hydroalcoholic extract were: 872.1 μl (DPPH), 186.7 μl (TEAC), 103 μM ET/100 ml extract (FRAP), 61 μM ET/100 ml extract (CUPRAC) and 297 μM ET/100 ml extract (SNP). While, of the antioxidant activity of *Ranunculus sceleratus* glycerol-ethanol extract were: 988.4 μl (DPPH), 250.7 μl (TEAC), 60 μM ET/100 ml extract (FRAP), 49μM ET/100 ml extract (CUPRAC) and 161 μM ET/100 ml extract (SNP)[39].

The extracts were screened for antioxidant assays including DPPH, ABTS and hydrogen peroxide assays. Ethanolic extract of *Ranunculus sceleratus* showed maximum H_2O_2 scavenging activity and optimum ABTS and DPPH radical scavenging activity, while, chloroform extract showed negligible antioxidant activity[46].

The shoot and root extracts of *Ranunculus sceleratus* were investigated for antioxidant activity using (DPPH) assay. The IC_{50} value of the methanolic extract (rich in phenols, saponins and tannins) was 0.37 mg/ml and 0.34 mg/ml for shoot and root methanolic extracts, respectively, compared to 0.15 mg/ml for catechol[45].

Anti-inflammatory effect

Ethanol (70%) extracts of the aerial parts and roots of three *Ranunculus* species were investigated for their suppressive effect on nitric oxide production in LPS-stimulated RAW 264.7 macrophages. The *in vitro* inhibitory properties were evaluated as nitrite concentration in LPS-stimulated RAW 264.7 macrophage cell line. All the samples induced concentration-dependent inhibitory effects, with *Ranunculus sceleratus* aerial parts extract being the most potent sample (IC_{50} = 22.08 ± 1.32 µg/ml), even more active than the reference compound, indomethacin[58].

The ability of *Ranunculus sceleratus* extract to modulate processes involved in inflammations was investigated in several models of acute inflammation induced by tetradecanoylphorbol acetate, arachidonic acid, and carrageenan, as well as in two models of delayed hypersensitivity induced by oxazolone and dinitrofluorobencene. The extracts were also assayed in models of eicosanoid and elastase release by intact cells. All the extracts showed anti-inflammatory *in vivo*. *In vitro*, non-polar extracts were able to inhibit eicosanoid production, whereas polar extracts enhanced the synthesis of 5(S)-HETE, LTB4 and 12(S)-HHTrE[59].

2.2.10. The bioaccumulation of trace metals

Ranunculus sceleratus accumulated high concentrations of Cu and Pb (27.7 and 9.9 mg/ kg), with a toxic concentration of Mn (2508.0 mg/ kg) in their roots compared to shoots. The bioaccumulation factor for some metals was greater than one, and in the following decreasing order: Ni (27.1) > Zn (20.0) > Cd (16.4) > Cu (7.7) > Mn (3.9) > Pb (3.6). The translocation factor of all analyzed trace metals was less than one. The ability of *Ranunculus sceleratus* to accumulate Mn, Ni, Cu, and Pb in its roots indicated the potential use of this species for phytostabilization of these metals (mainly Mn) in contaminated water bodies[60].

2.2.11. Toxicity

Whole plant is poisonous, toxic constituents are protoanemonin (anemonol) and ranunculin. Ranunculin is hydrolyzed into protoanemonin upon crushing of plant tissue. Protoanemonin is an irritant to skin, eyes and mucosal surface; it binds sulphydryl groups and disrupts disulphide bonds, leading to disruption of skin architecture and formation of bulla. Contact with protoanemonin causes dermatitis, burning and itching with accompanying rash and blisters. If the leaves are chewed by humans or beasts, blisters may form on the lips and face. The toxic oil is also a serious eye irritant. In swallowing of some buttercups, patient will complain abdominal pain, diarrhea, vomiting, dizziness and even paralysis[61].

3. Conclusion

In this review, the constituents and the pharmacological activities of *Ranunculus arvensis*and *Ranunculussceleratus* were discussed in comparison to their toxicity to encourage the researchers to conduct further pharmacological and toxicological studies on these species.

Compliance with ethical standards

Acknowledgments

We acknowledged the dean of Thi qar college of medicine, for the scientific support.

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