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Revisión | Review

Traditional usages, botany, phytochemistry, biological activity and toxicology of *Tropaeolum majus* L. - A review

[Usos tradicionales, botánica, fitoquímica, actividad biológica y toxicología de *Tropaeolum majus* L. - Una revisión]

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Abstract: *Tropaeolum majus* presents medicinal, nutritional and ornamental value. Plant extracts and fractions have been found to exhibit diuretic, antihypertensive, anti-inflammatory, antimicrobial and antioxidant activities. Moreover, protective effects on blood and liver, scurvy's treatment, antithrombin activity and prevention against macular degeneration have also been observed. *T. majus* contains biologically active compounds such as flavonoids, glucosilonates, fatty acids, essential oil, chlorogenic acid, aminoacids, cucurbitacins, proteins and carotenoids. Acute and subchronic studies demonstrated a lack of toxic effects, but the extracts of this plant can have deleterious consequences during the pregnancy. The revised databases were SciELO, PubMed, ScienceDirect and Portal da Capes, considering studies between 1963 and 2014 and by searching for terms like *Tropaeolum majus*, Tropaeolaceae, *Tropaeolum majus* constituents, *Tropaeolum majus* use and *Tropaeolum majus* toxicity.

Keywords: *Tropaeolum majus*, biological activities, chemical constituents, traditional usages, toxicity

Resumen: *Tropaeolum majus* presenta valor medicinal, alimenticio y ornamental. A partir del extracto y las fracciones de la planta se han encontrado actividades biológicas, que incluyen efecto diurético, antihipertensivo, anti-inflamatorio, antimicrobiano y antioxidante. Además, efectos protectores sobre la sangre y el hígado, tratamiento del escorbuto, actividad antitrombina y prevención contra la degeneración macular. *T. majus* contiene compuestos biológicamente activos como flavonoides, glucosilonates, ácidos grasos, aceite esencial, ácido clorogénico, aminoácidos, cucurbitacinas, proteínas y carotenoides. Estudios de toxicidad aguda y subcrónica demostraron una falta de efectos toxicológicos, pero los extractos de esta planta pueden tener consecuencias perjudiciales durante el embarazo. Las bases de datos revisadas fueron SciELO, PubMed, ScienceDirect y Portal da Capes, teniendo en cuenta los estudios entre 1963 y 2014 y mediante la búsqueda de términos como *Tropaeolum majus*, Tropaeolaceae, *Tropaeolum majus* constituyentes, *Tropaeolum majus* usos y *Tropaeolum majus* toxicidad.

Palabras clave: *Tropaeolum majus*, actividad biológica, compuestos químicos, toxicidad

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INTRODUCTION

The utilization of natural products, mainly flora in therapeutic purposes, is an ancient practice transmitted between successive generations (Andrade *et al*., 2007). As illustrated by the pharmacopoeias from the nineteenth century, therapeutic resources consisted primarily of plant extracts. Concurrently with the advancement of medicine, the isolation of active constituents derived from raw vegetable materials began around the turn of the twentieth century (Veiga *et al*., 2005).

Despite the great advances of allopathic medicine in recent years, plants still remain an important alternative to health promoting. This is observed due to the obstacles in the use of traditional medicine (Ouedraogo *et al.,* 2012). In countries where modern healthcare is limited or unavailable, the traditional use of medicinal plants is often widely praticed (Agra *et al*., 2007).

The data presented below were obtained after researches using SciELO, PubMed, ScienceDirect and Portal da Capes as databases.

Botany

Tropaeolum majus L. is an annual and rapid-growing plant that belongs to the Tropaeolaceae family, colloquially known as chaguinha, capuchinha and nastúrcio in Brazil (Lorenzi & Matos, 2002). Originally from Peru to Mexico, it is able to grow in many parts of the world due to its rusticity and adaptability (Panizza, 1997). The stem is soft, winding, long and fleshy. Its leaves are rounded, greenish blue in color and fixed by the lower parts of the stalks's center. The flowers are hermaphroditic, zygomorphic, showy, tapered and isolated along the peduncle, while the corolla is pentamerous, with coloring that ranges from yellow to dark red. The chalice is divided at the apex into five sepals and the fruits are formed by three small achenes, greenish coloring (Ferri *et al*., 1981; Silva *et al*., 2009). Each fruit contains three seeds, which fall to the ground and spontaneously germinate (Ortiz de Boada & Cogua, 1989).

Microscopic analysis of leaves showed that the epidermis is uniseriate and amphistomatic. In the abaxial epidermis, cells are smaller, the winding is more pronounced and uniseriate glandular hairs occur with 3-6 cells and tapered ends. The anomo and anisocytic stomata are xerophytic and the substomatal camera is bigger in adaxial epidermis. The mesophyll has a unistratified palisade parenchyma and a spongy parenchyma formed by 5-6 layers of round cells with space gaps. Also, microscopic analysis of bark showed thick cuticle. The epicuticular formations and epidermal cells tend to be rectangular. The chollenchyma (angular type) is formed by two layers of cells underlying the epidermis. The xylem has parenchymatous cells and the bone marrow is the major part of the stem (Zanetti *et al.,* 2004).

Phytochemistry

There are many chemical constituents isolated from *T. majus*, including polyphenols, glucosilonates and fatty acids. In this section, we describe the major chemical components of this plant.

Flavonoids

Several flavonoids have been isolated from *T. majus*. Koriem *et al* analyzed the flavonoids present in the leaves and flowers of *T. majus*'s methyl alcohol extract with liquid chromatography/mass spectra (LC/MS). The results showed a greater amount of a kaempferol glucoside (9.40 mg/100 mL extract), followed by isoquercitroside (2.25 mg/100 mL extract) and quercetol 3-triglucoside (1.17 mg/100 mL extract) (Koriem *et al*., 2010). Using electrospray ionization-mass spectrometry (ESI-MS) and high performance liquid chromatography (HPLC-UV) to analyze the leaf extracts, Gasparotto *et al.* (2011a) obtained, as the major components of the fraction eluted with water and ethanol, isoquercitrin and kaempferol glucoside (Gasparotto *et al*., 2011a).

Bazylko *et al.* (2013), demonstrated the presence of quercetin-3-O-glucoside (isoquercitrin) and kaempferol-3-O-glucoside (astragalin) in the aqueous extract of the *T. majus*'s herb. Also, the presence of quercetin and kaempferol derivatives were detected (Bazylko *et al*., 2013). In another work from the same research group, a higher content of flavonoids was identified in the hydroethanolic extract and aqueous extract of leaves and flowers (26.0 mg/g and 15.2 mg/g, respectively), follwed by the herb juice (11.2 mg/g). In a similar pattern, the content of total phenols was 35.6 mg/g in the hydroethanolic extract and 29.5 mg/g in the aqueous extract, followed by herb juice (19.5 mg/g) (Bazylko *et al*., 2014).

Isoquercitrin is a natural flavonoid glucoside, quercetin analog, that has been found to have a wide range of biological properties (Razavi *et al*., 2009), such as diuretic effect; anti-inflammatory action; antioxidant activity, decreasing ROS levels; reducing capability of lipid peroxidation and inhibition of adipocyte differentiation (Rogerio *et al*., 2007; Gasparotto *et al*., 2011a; Li *et al*., 2011; Lee *et al*., 2011). Lipid peroxidation is a chain reaction of the polyunsaturated fatty acids of cell membranes, which undergo alterations in permeability, fluidity and integrity due to production of free radicals. These damaged cells are predisposed to well known comorbidities, such as systemic arterial hypertension, dyslipidemia, thromboembolic events, diabetes mellitus and cancer (Mahattanatawee *et al*., 2006). Many flavonoids are antioxidants, hence some of the compounds found in *T. majus* may act to prevent cell degeneration (Bohm *et al*., 1998). For example, kaempferol acts as a proton radical scavenger (DPPH scavenging assay), hydroxyl radical scavenger (deoxyribose degradation assay) and metal chelating agent (Singh *et al*., 2008).

Glucosilonates

Glucosilonates are hydrophilic compounds that are chemically and thermally stable. Its hydrolysis occurs due to an enzymatic reaction mediated by endogenous enzyme myrosinase (ß-thioglucosidase). This enzyme occurs in plants containing glucosilonates, but in separate compartments. When the tissue gets damaged, e.g. by the action of fungi, chewing or cutting, the glucosilonates are put in contact with myrosinase, thereby releasing benzyl isothiocyanate (Bones & Rossiter, 1996).

The main glucosilonates found in *T. majus* are glucotropaeolin (Figure 1) and sinalbin. Koriem *et al* obtained both constituents from the leaves and flowers of *T. majus*’s methyl alcohol extract (1.65 mg of glucotropaeolin/100 mL extract and 12.54 mg of sinalbin/100 mL extract) (Koriem *et al*., 2010). Using HPLC method, Bazylko *et al.* (2013) also showed the presence of glucotropaeolin in *T. majus*'s hydroethanolic extract obtained at 90° C (Bazylko *et al*., 2013). Interesting, in another work from the same group, the analysis showed a lack of glucotropaeolin in the aqueous extract and juice. Moreover, only traces of glucotropaeolin in the hydroethanolic extract were observed (Bazylko *et al*., 2014).

Koriem *et al.* (2010), dosed benzyl isothiocyanate in the methyl alcohol extract of *T. majus*’s leaves and flowers, founding 20.24 mg/100 mL extract (Koriem *et al*., 2010). Benzyl isothiocyanate has important physiological roles. It stimulates the chemo-protective mechanisms, but, depending on its concentration, can also induce cellular stress. Act as inducers of phase 2 enzymes of detoxification mechanism and inhibit phase 1 enzymes, thereby accentuating the cell performance in chemical detoxification. *In vitro* studies have also shown antimicrobial and anthelmintic activities. Moreover, it has an important anticancer function, increasing the occurrence of apoptosis of cancer cells (Kermanshai *et al*., 2001; D`agostini *et al*., 2005; Morant *et al*., 2008; Volden *et al*., 2008; Sofrata *et al*., 2011).

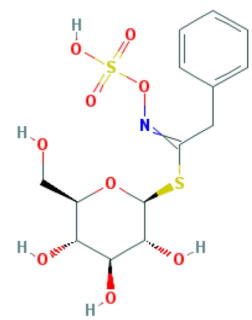

Figure 1
Chemical structure of glucotropaeolin

Fatty acids

Koriem *et al.* (2010), dosed the fatty acids content in the leaves and flowers of *T. majus*’s methyl alcohol extract through liquid chromatography/mass spectra (LC/MS). The phytochemical screening showed a higher concentration of linoleic acid (1.18 mg/100 mL extract), followed by oleic acid (0.71 mg/100 mL extract) and erucic acid (0.22 mg/100 mL extract) (Koriem *et al*., 2010).

The essential fatty acids, oleic and linoleic, have important functions to the organism. They can help to prevent heart disease, decrease blood clotting, suppress cancer formation, suppress a wide range of allergic mediators, and exert neuroprotective action, among others (Chin *et al*., 1992; Bemelmans *et al*., 2002; Martínez-González & Bes-Rastrollo, 2006).

Oleic acid is called as an omega 9 acid. It participates in the human metabolism, as an antioxidant and playing fundamental role in the synthesis of hormones (Bressan *et al*., 2009).

Also, linoleic acid, called as an omega 6 acid. It is a precursor of arachidonic acid, having important role in the production of a series of lipid mediators, the eicosanoids, which are synthesized through the arachidonic acid cascade (James *et al*., 2000). It is necessary to keep cell membranes, brain functions and the transmission of nerve impulses under normal conditions.These fatty acids are known to participate in the transfer of atmospheric oxygen to blood plasma, the cell division and the synthesis of hemoglobin (Youdim *et al*., 2000).

Other constituents

In addition to the compounds already mentioned above, other components of *T. majus* have been reported, including carotenoids, terpenoids, ascorbic acid, anthocyanins, esters of quinic acid with cinnamic acids (chlorogenic acids and p-coumaroylquinic acids), sugar and minerals (Harbone, 1963; Ferri *et al*., 1981; Niizu & Rodriguez-Amaya, 2005; Garzón & Wrolstad, 2009; Bazylko *et al*., 2013).

According to Niizu and Rodriguez-Amaya (2005), eight carotenoids were identified in the flowers of *T. majus*: violaxanthin, antheraxanthin, lutein, zeaxanthin, zeinoxanthin, β- cryptoxanthin, α-carotene and beta-carotene. In the yellow flowers, 450 µg/g lutein, traces of violaxanthin and β-carotene were detected, while neoxanthin was not found. In the orange flowers, 350 µg/g lutein were detected, also traces of violaxanthin and β-carotene, and levels not detected of neoxanthin. Interesting, 136 µg/g lutein, 74 µg/g violaxanthin, 69 µg/g β-carotene and 48 µg/g neoxanthin were measured in the leaves (Niizu & Rodriguez-Amaya, 2005).

The yield of anthocyanin content of *T. majus* is unknown. Harbone tried to report the main pigment presented in the orange petals of *T. majus*'s flowers as pelargonidin 3-sophoroside (Harbone, 1963). Garzón and Wrolstad (2009), dosed the anthocyanins content in the petals of orange flowers of *T. majus* and found 72 mg anthocyanin/100 g flowers (Garzón & Wrolstad, 2009). Also, through Sudan III analysis, the presence of essential oils was characterized in all parenchymatics formations (Zanetti *et al*., 2004). The oil produced by the seeds, known worldwide as Lorenzo's oil, is used to treat a severe and degenerative disease called adrenoleukodystrophy (Carlson & Kleiman, 1993).

Biological activity

With a wide spectrum of biological and pharmacological effects, *T. majus* has been used as a tradional medicine for many years. As such, researchers have tested the crude exctracts and fractions for a variety of biological activites. Some of those studies are discussed below.

Traditional usages

It is popularly used as antiseptic, diuretic, purgative, hair tonic, antiscorbutic, anti-inflammatory, antihypertensive and antidepressant. In addition, it is applied in the cleaning of skin, eyes and in the treatment of skin disorders, furunculosis, acne, pulmonary disorders, amyotrophic lateral sclerosis, psoriasis, eczema and scrofula (Boorhem, 1999; Lorenzi & Matos, 2002; Ferreira *et al*., 2004; Lourenço *et al*., 2011; Messias *et al*., 2015). Moreover, this plant is widely cultivated for ornamental purposes and, also, it has pleasant aroma and spicy flavor, similar to the characteristics found in watercress. Due to its high nutritional value, particularly rich in sulfur, its leaves, floral buttons and flowers are used in salads (Bown, 1995; Panizza, 1997; Boorhem, 1999; Vaz & Jorge, 2006).

Diuretic effect and its mechanisms

Several studies, both *in vitro* and *in vivo*, have demonstrated the diuretic action of *T. majus* (Binet, 1964; Goos *et al*., 2006; Barboza *et al*., 2014).

Gasparotto *et al.* (2011a), tested the diuretic effect of the semi-purified fraction obtained from hydroethanolic extract (TMLR) of *T. majus*'s leaves and its component, the flavonoid isoquercitrin. The treatment with a single dose of the TMRL (100 mg/kg) significantly increased diuresis after 6, 8, 15 and 24 hours. The total volume of urine measured at 6 and 24 hours in TMRL-treated animals were 2.22 mL and 3.97 mL, respectively, while the urinary output in the control group, at the same times, were 1.02 mL and 2.53 mL, respectively. The single administration of isoquercitrin (10 mg/kg) also increased diuresis when compared to the control group. The volume of urine, after 4 hours, was 1.63 mL in the isoquercitrin group versus 0.85 mL in the control group (Gasparotto *et al*., 2011a).

The effects of acute treatments with hydrochlorothiazide (HCTZ), TMRL (100 mg/kg) and isoquercitrin (10 mg/kg) on electrolyte levels were also evaluated. All tested substances increased the excretion of the Na^+, however, only the HCTZ group presented high amounts of K^+ in the urine. The consequence of longer treatment times was also studied, the daily administration of TMLR (100 mg/kg) and isoquercitrin (10 mg/kg) for 7 days significantly increased diuresis after the first day of treatments, such that the cumulative urinary flow increased from 2.53 mL in control animals to 3.97 mL and 4.58 mL in rats treated with TMLR and isoquercitrin, respectively. Moreover, the Na^+ excretion in urine was increased in both treatments at days 1, 5, 6 and 7, but K^+ levels remained unchanged. The hydrochlorothiazide group significantly increased the K^+ urinary excretion. The authors attribute the diuretic activity mainly due the presence of isoquercitrin in the TMRL fraction (Gasparotto *et al*., 2011a).

Another work from the same research group tested the diuretic effect after the oral administration of the ethanolic extract of *T. majus*'s leaves (HETM), its purified fraction (TMLR) and isoquercitrin (ISQ), comparing the results with drugs well known as diuretics (furosemide/FURO, hydrochlorothiazide/HCTZ, acetazolamide/ACTZ and spironolactone/SPIRO). The urinary output measured in HETM, TMLR and ISQ groups were similar to those found in ACTZ, SPIRO and FURO groups and slightly less than in HCTZ group. Compared to the extracts of *T. majus* (HETM and TMLR), the HCTZ treated animals presented higher amounts of Na^+ in the urine. Both ACTZ and HCTZ treatments increased urinary excretion of K^+ by, respectively, 72% and 88%. This parameter remained unchanged in animals treated with *T. majus*'s extracts and ISQ groups. The urinary Cl^- excretion was 12.48 mmol/l/15 h in the SPIRO group (50 mg/kg), 12.35 mmol/l/15 h in the TMLR group (100 mg/kg), 11.20 mmol/l/15 h in the HETM group (300 mg/kg) and 10.31 mmol/l/15 h for the group control. However, the measured values were quite different for FURO 10 mg/kg (26.33 mmol/l/15 h) and HCTZ 10 mg/kg (20.17 mmol/l/15 h) (Gasparotto *et al*., 2012).

According to the authors, the general profile of the diuretic action indicates that the effect of *T. majus* extracts and ISQ are close to the one induced by spironolactone. They also attribute the diuretic effect to the inhibition of the angiotensin converter enzyme and subsequent increase in the bioavailability of bradykinin, PGI_2 and nitric oxide. Also, an inhibitory effect on Na^+/K^+-ATPase may be related to the increased diuresis. Similar to spironolactone, the reduction in serum aldosterone, associated with hypotensive action, may increase hydrostatic pressure in renal arterioles, being responsible for the diuretic and natriuretic effects observed. Low amounts of potassium and/or other metals were observed in *T. majus*, a fact that led the authors to discard the possibility that an osmotic mechanism could be related to the diuretic effect (Gasparotto *et al*., 2012).

Antihypertensive action

Gasparotto *et al*. (2011b), tested the antihypertensive effects of isoquercitrin, hydroethanolic extracts of *T. majus* (HETM) and the semi-purified fraction (TMLR). After 1.5 hours of the oral treatment with HETM 10 and 300 mg/kg, the basal mean arterial pressure (MAP) in normotensive rats was reduced in ~13 mm Hg, in a dose and time-dependent manner. Similary, the oral administration of TMLR 12.5 and 100 mg/kg caused hypotensive effects, with reduction values of 17.94 and 20.77 mm Hg, respectively. However, none of the treatments were able to reduce the heart rate. Analyzing the hypotensive effects of isoquercitrin in normotensive rats, the study showed that the intravenous administration of isoquercitrin (0.5 - 4 mg/kg) was able to cause a reduction in MAP (dose-dependent manner), with minor influences on heart rate. The intraduodenal treatment, with TMLR (50 mg/kg) and HETM (100 mg/kg), presented antihypertensive and hypotensive effects, with MAP reduction of 18.77 and 14.14 mm Hg for SHR and WKY rats, respectively (Gasparotto *et al*., 2011b).

Regarding the measurement of serum angiotensin converting enzyme (ACE), the oral administrations of HETM (0 - 300 mg/kg), TMLR (25 - 100 mg/kg) and isoquercitrin (5 - 10 mg/kg) were able to reduce the serum activity of ACE by 20% and 24% at 100 and 300 mg/kg of HETM, respectively. Rats treated with TMRL at 50 and 100 mg/kg exhibited a reduction in ACE activity of 28% and 30%, respectively. Futhermore, the study showed that the intravenous administration of isoquercitrin (4 mg/kg) caused a 34% reduction in the hypertensive response of angiotensin I in normotensive rats and had no significant effect in the hypotensive effects of bradykinin. The authors state that the reduction in blood pressure cannot be directly related to any cardiac effect since the hypotension which was verified after the treatments with HETM and TMLR, was not followed by significant reduction in the heart rate of the animals tested. Also, they hypothesize that the hypotensive effect could be related to the isoquercitrin present in *T. majus* (Gasparotto *et al*., 2011b).

Antimicrobial activity

Benzyl isothiocyanates are recognized as potential antimicrobial agents (Masuda *et al*., 2009; Jang *et al*., 2010; Sofrata *et al*., 2011; Dufour *et al*., 2012). Bazylko *et al.*, tested the activity of *T. majus*'s herb extracts (aqueous and hydroethanolic) against *Staphylococcus aureus*, *Bacilus subtilis*, *Micrococcus luteus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Bordetella bronchiseptica*. No antimicrobial activity was detected and the authors correlate it to the low content of benzyl isothiocyanate in the extracts (Bazylko *et al*., 2013).

On the other hand, the antimicrobial activity of the fractions of the ethanolic extract of *T. majus* were determined by bioautography using Gram-positive and Gram-negative bacteria, besides amoxicillin as positive control. As a result, the hexane and chloroform fractions presented inhibition zones for all microorganisms tested (*Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae* and *Salmonella setubal*) (Zanetti *et al*., 2003).

Antioxidant activity

Some studies have studied the antioxidant action of *T. majus* (Machado, 2008; Bazylko *et al*., 2013; Vieira, 2013). From the orange flowers, Garzón and Wrolstad (2009), tested the antioxidant capacity of *T. majus* determining the ABTS radical cation scavenging activity, through the method described by Re *et al.* (1999), and the DPPH free radical scavenging activity according to the method described by Hsu *et al.* (2006). The results showed that *T. majus*'s orange flowers were able extinguish the radicals ABTS and DPPH, with the ABTS radical scavenging activity being higher than the DPPH radical scavenging activity (Re *et al*., 1999; Hsu *et al.*, 2006; Garzón & Wrolstad, 2009).

Bazylko *et al.* (2014), determined the antioxidant activity of *T. majus* by analyzing the aqueous and hydroethanolic extracts of the leaves and flowers and the fresh herb juice through the DPPH radical scavenging activity, and the evaluation of ROS production in cellular model by chemiluminescence and oxidation of human neutrophils. The tested extracts and juice had a low DPPH scavenging activity at a concentration of 100 µg/mL, being 24.1%, 37.5% and 34.7% for the aqueous extract, hydroethanolic extract and juice, respectively. About ROS generation, the extracts showed stronger antioxidant activity against H_2O_2 and O_2^-, while the juice presented significant activity only against O_2^-. In the *ex vivo* model of human neutrophils oxidation, the hydroethanolic extract showed a stronger inhibition of ROS production, and the aqueous extract showed weaker inhibitory action. However, the weakest activity was observed with the juice (Bazylko *et al.*, 2014).

Other actions

Protective effects on the blood and livers of rats against diethyl maleate toxicity, treatment of scurvy, antithrombin activity and prevention against macular degeneration were observed because of the carotenoids found in the plant (Niizu & Rodriguez-Amaya, 2005; Santo *et al*., 2007; Koriem *et al*., 2010). In the hormonal system, the hydroethanolic extract obtained from *T. majus*'s leaves does not affect the *ex vivo* uterine contractility of pregnant rats induced by oxytocin or arachidonic acid. Moreover, it has a lack of *in vivo* estrogenic or anti-estrogenic activity, indicating that *T. majus* does not modulate estrogen responses *in vivo* and has no influence on uterine contractility. It is also unable to elicit androgenic activities, block the effects of testosterone on androgen-sensitive tissues such as prostate, seminal vesicle, glans penis and levator ani/bulbocavernosus muscle (Lourenço *et al.*, 2012). Also, from aqueous and hydroethanolic extracts of *T. majus*, Bazylko *et al.* (2013), examined the potential anti-inflammatory activity, and evaluated the inhibition of cyclooxygenase 1 (COX1) and hyaluronidase. All extracts showed inhibition of cyclooxygenase 1 activity, with the extracts from freeze-dried herbs exhibiting strong action at a concentration of 50 µg/mL an effect comparable to that of 2 µM indomethacin. However, none of the extracts acted as inhibitors of hyaluronidase (Bazylko *et al*., 2013).

Toxicity

The number of reports on the *T. majus* toxicity show a safe usage, except during pregnancy.

Zanetti *et al.* (2003), tested the acute toxicity of the aqueous and hydroethanolic extracts of *T. majus*'s leaves and bark in mice, using the method described by Brito (1994). At doses of: 625, 1250, 2500 and 5000 mg/kg, the extracts did not show any signs of toxicity, such as deaths, depression, excitement, convulsions, salivation, piloerection, tearing, defecation abnormalities or effects on breathing and locomotion (Zanetti *et al.,* 2003; Brito, 1994). Similar to the results obtained by Gasparotto *et al.* (2009), in which, no signs of acute toxicity were found in male and female rats, after the oral administration of *T. majus* hydroethanolic extract at a dose of 5000 mg/kg, or intraperitoneally, at doses of 1000 and 3000 mg/kg (Gasparotto *et al.,* 2009).

Through the hydroethanolic extract of *T. majus*'s leaves, Gomes *et al.* (2012), evaluated the oral subchronic toxicity in Wistar rats. Signs of toxicity, like diarrhea, piloerection, shivering, salivation and convultions, were not observed. Also, none of the animals died during the 28 days of treatment at doses of: 75, 375 and 750 mg/kg, or vehicle. No statistical differences were seen in the relative weight of liver, kidneys or spleen among any of the groups. Moreover, the results indicate an absence of hematological and biochemical disorders. Moreoever, no histopathological alterations were related to the treatments. These results indicate an absence of oral toxicity due to subchronic treatment with *T. majus* (Gomes *et al.,* 2012).

On the other hand, Lourenço *et al.* (2014), studied the effect of the hydroethanolic extract of *T. majus*'s leaves (HETM) on the embryonic development when administered to pregnant rats during the one-cell-blastocyst period, which comprehends the phases of tubal transit and implantation. Although no signs of maternal toxicity were seen, the daily treatment with HETM, at doses of 300 mg/kg, significantly increased both, the serum dehydroepiandrosterone (DHEA) and estradiol levels, while progesterone was not affected. It is known that elevated levels of DHEA can cause a strong increase in embryo implantation failure by interfering with proper growth, development and differentiation of the endometrium into a decidua. So, the ability of *T. majus*'s extract to increase the concentration of this hormone may be related to the reduction of proper embryo implantation in the early stages of pregnancy, thereby inhibiting it (Lourenço *et al.,* 2014).

CONCLUSIONS

The flavonoid isoquercitrin, isolated from *T. majus*'s extracts, showed a wide range of biological activities, including diuretic, antioxidant and antihypertensive actions. Another flavonoid that was isolated, kaempferol, also demonstrated antioxidant activity.

Other biological activities can also be related to *T. majus*, as the antithrombin and anti-inflammatory activities, the protective effects on blood and liver against diethyl maleate toxicity and the use of its extracts in the treatment of scurvy.

Due to the widespread traditional use of *T. majus*, its chemical composition, biological activity and the possibility of toxic effects during the pregnancy, further investigation into the plant’s medicinal properties may be warranted.

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