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AN ALTERNATIVE HEPATOPROTECTIVE AND ANTIOXIDANT AGENT: THE *GERANIUM*

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Abstract

Background: The *Geranium* genus is taxonomically classified within the family Geraniaceae Juss, which includes 5-11 genera and nearly 750 species in total. The best-known genera of this family are *Geranium*, consisting largely of wild plants, and Pelargonium, consisting largely of ornamental plants. Traditional uses include as an antiseptic in wounds and as an antipyretic by infusion of the plant.
Methods: This paper summarized previous and recent reports of the hepato-protective activities of *Geranium* genus used in traditional medicine.
Results: Currently, eight different species of *geraniums* belonging to the family Geraniaceae have been identified in Hidalgo State in Central Mexico, and no chemical or pharmacological studies have been carried out in any of these eight species. All phytochemical studies on these species indicate the presence of polyphenolic compounds, including tannins, which are characterized as water-soluble compounds with molecular weights between 500 and 30,000 g/mol.
Conclusion: These and other compounds warrant the exploration of the Germanium genus for uses related to ethanol-induced hepatotoxicity.

Key words: *Geranium*, Polyphenolic compounds, Tannins, Ethanol.

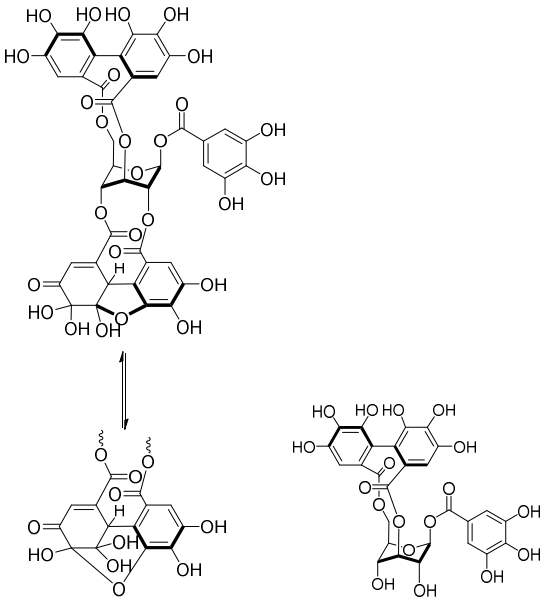
Introduction

Alcohol, one of the oldest drugs used by humans, is a dietary component that is usually consumed for its psychophysical effects. However, long-term alcohol consumption may cause damage to vital organs, including gastrointestinal, endocrine, and cardiovascular organs as well as the central nervous system (Preedy et al, 1999).

Alcohol is also responsible for many hepatic injuries, such as hepatic steatosis, alcoholic hepatitis, and cirrhosis. The mechanism of liver damage induced by alcohol is multifactorial: on the one hand, the acetaldehyde generated by the metabolism of alcohol favors lipid peroxidation; on the other hand, chronic alcohol ingestion increases oxygen consumption, causing zones exposed to this oxygen gradient to become more vulnerable to necrosis.

There are no specific allopathic medicines that are utilized as hepatoprotectors, although research is being conducted on certain drugs such as Rimonabant, a selective endocannabinoid (CB1) receptor antagonist that inhibits the pharmacological effects of cannabinoid agonists *in vitro* and *in vivo* and has hepatoprotective activity against hepatotoxicants such as ethanol. It has been observed that the administration of Rimonabant at doses of 2.5, 5, and 10 mg/kg attenuates the increase of serum enzymes due to ethanol and causes a subsequent recovery toward normalization similar to that of silymarin treatment (Arshad, 2010). Additionally, steroids such as corticosteroids are being examined for their hepatoprotective action (Robert et al, 2010). In general, herbal drugs are more widely employed than allopathic drugs as hepatoprotectors because they are inexpensive, culturally accepted, exhibit a better compatibility with the human body, and have minimal side effects (Tripathi, 2008); this is also the case for the treatment of hepatic disease. There are many plants reported to act as hepatoprotectors, such as *Silybum marianum* (St. Mary thistle), *Andrographis paniculata* (kalmegh), *Swertia chirata Buch Ham* (Chirata), *Cichorium intybus* (Kasani), *Picrorhija kurroa* (Katuki), and *Boerhavia diffusa* (Punarnava) (Adewusi, 2010; Kamble et al, 2008; Kokate, 2008); all of these have been studied to identify their different compounds. Among them, glycosides, flavonoids, triterpenes, and phenolic compounds, have been identified as classes of compounds possessing hepatoprotective activity. Flavonoids and phenolic acids have also shown antibacterial, antifungal, antiviral, antineoplastic, hepatoprotective, immunomodulating, and anti-inflammatory properties and are of particular interest due to their proven beneficial therapeutic use in patients with allergies, asthma, diabetes, hypertension, and microbleeding, among other conditions. It is noteworthy that these pharmacological effects are mainly associated with the antioxidant activities of these compounds (Havsteen, 1983) and that further studies, including clinical trials, need to be carried out to ascertain the safety of these compounds as alternatives to conventional drugs for the treatment of liver diseases.

Although a variety of genera with hepatoprotective properties have been characterized, there are many species, such as the *geranium* (Gayosso-De-Lucio et al, 2010; Gayosso-De-Lucio et al, 2009), on which no studies demonstrating this capacity are available. One of the major components of these plants is geranium, which was described by its discoverer as a crystallizable tannin (Okuda, 1989). Geraniin (1) inhibits angiotensin converting enzyme (Kameda et al, 1987; Ueno et al, 1988), the reverse transcriptase of RNA tumor viruses (Kakiuchi et al, 1985), Herpes simplex virus (HSV)-1 and HSV-2 multiplication at various magnitudes of potency; exhibits antihypertensive activity; and is an excellent antioxidant (Fujiki et al, 2003). A derivative of geraniin, corilagin (2) (Okuda et al, 1975), has also demonstrated antimicrobial activity, among other potentially advantageous properties.



Geraniin (1) Corilagin (2)

The *Geranium* Species and Its Compounds

Within the classification of the *Geranium* genus, there are 423 accepted species that are distributed in three subgenera: Erodioidea, *Geranium*, and Robertium. To date, eight different species have been classified within the state of Hidalgo in Central Mexico (Pérez Escandónet al, 1998), none of which have associated chemical or pharmacological studies. Some species of *Geranium* act as hypotensive agents, mild astringents, diuretics, hepatoprotective agents, antioxidants, anti-inflammatory agents, or antiviral agents. All phytochemical studies on these species indicate the presence of tannins, water-soluble polyphenolic compounds with molecular weights ranging between 500 and 30,000 g/mol and with special properties such as the ability to precipitate alkaloids, gelatin, and other proteins (Okuda et al, 1989). At present, tannins are well known because of their antioxidant properties. Tannin-protein complexes in the gastrointestinal tract provide persistent antioxidant activity. The present review considers different compounds isolated from species within *Geranium* and the hypothesis that exploring the genus further could reveal a useful hepatoprotective agent for alcohol-related liver damage. **Figure 1** shows a global map of the culture of the different species of *geranium*.

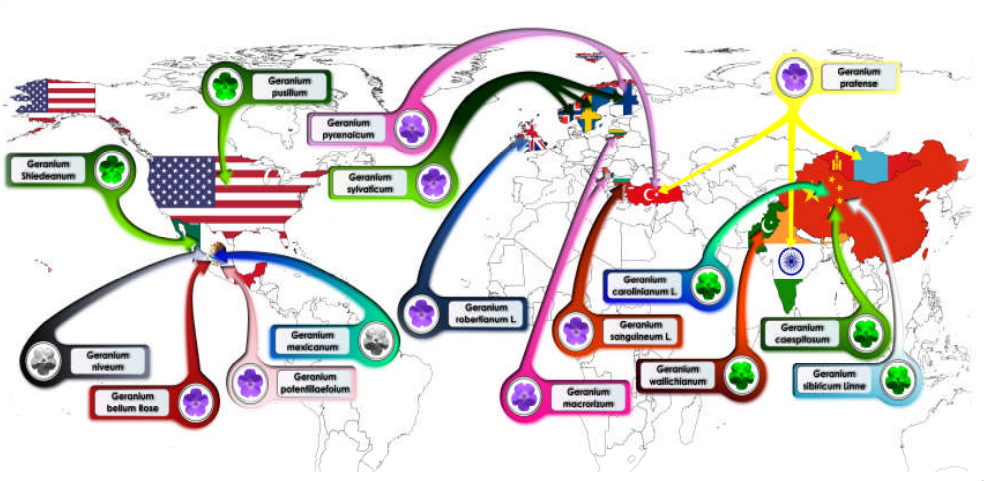
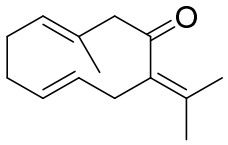


Figure 1: World map and cultivation of the different genera of *Geranium*.

The species *Geranium macrorrhizum* presented significant hypotensive activity in anesthetized cats (Radulović et al, 2012). In addition, the compound responsible for the antioxidant activity of this species, germacrone (3), was isolated and determined to be a precursor of pheromones. Methanol extracts administered with the highest antioxidant potential demonstrated significant dose-dependent hepatoprotective action against CCl_4-

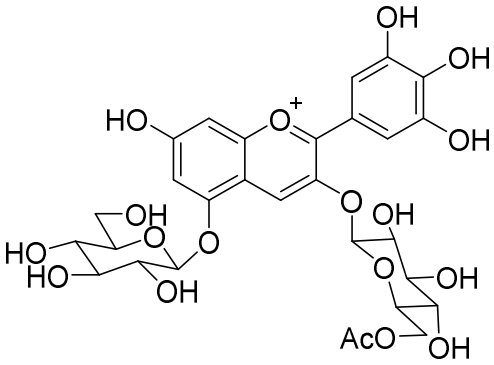
induced liver damage in both decreasing liver transaminase and bilirubin levels and reducing the extent of morphological liver malformations. The methanol extract from the leaves of this plant displayed very strong antibacterial activity, especially against *Staphylococcus aureus*, with low minimal inhibitory and bactericidal concentrations.



Germacrone (3)

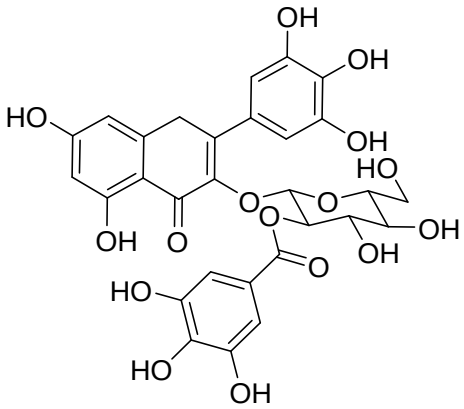
Geranium robertianum L., a well-known species and one of the most variable in Britain, has been utilized under conditions in which increased diuresis is required, such as in cystitis, urethritis, pyelonephritis, gout, hypertension, and edema. At present, the phytochemistry of this *geranium* is relatively well known, and its most studied active compounds include tannins, volatile oils, flavonoids, and polyphenols (hyperoside, ellagic acid, isoquercitrin, quercitrin, kaempferol, caftaric acid, and rutoside). Additionally, infusions and decoctions prepared from the leaves of this *geranium*, Robert herb, or Red Robin are described as antihyperglycemic and are commonly used in Portuguese herbal medicine (Cunha et al, 2009). Consumption of the extract of *G. robertianum* increased the coupling effectiveness between the oxidative and phosphorylative systems in Goto-Kakizaki (GK) rats, as demonstrated by a considerably higher respiratory control ratio (RCR) (Ferreira et al, 2010).

Geranium sylvaticum. Recently, extracts of *G. sylvaticum* were studied (Andersen et al, 1995) for their antioxidant potential. All tested extracts possessed strong antioxidant activity and will be subjected to further investigations. 3-O-(6-O-acetyl-•-D-glucopyranoside)-5-O- β -D-glucopyranoside of malvidin (4) was isolated from the flowers of *Geranium sylvaticum* (Akdemir et al, 2001).



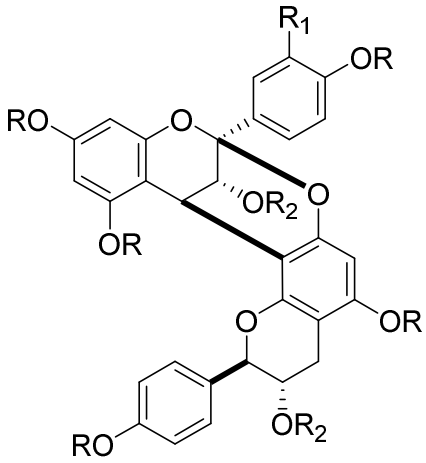
Malvidin 3-*O*-(6-*O*-acetil-β-D-glucopiranóside)-5-*O*-β-D-glucopiranoside (4)

Geranium sanguineum L. demonstrated significant inhibitory activity against the influenza virus and herpes simplex and is also traditionally used for the treatment of skin lesions and for the relief of pruritus and itching. The methanolic extract of *Geranium pratense* inhibited the action of amylase enzyme in mouse plasma, and to the best of our knowledge, the 3-O-(2-O-galloyl)-•-D-glucopyranoside myricetin (5) was isolated for the first time (Maldonado et al, 2005).

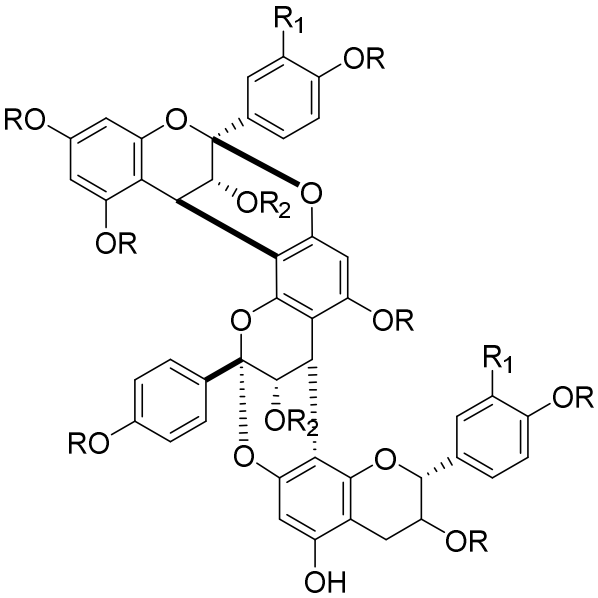


Miricetin 3-*O*-(2-*O*-galoil)-β-D-glucopiranóside (5)

Geranium niveum is widely used by the Tarahumara Indians of northern Mexico and is a species rich in proanthocyanidins and other phenolics (Calzada et al, 1999). Previous *in vitro* assays have demonstrated that proanthocyanidins exhibit anti-inflammatory, antiviral, antibacterial, enzyme-inhibiting, antioxidant, and radical-scavenging properties. From the roots (Adewusi and Afolayan, 2010) of this species, new proanthocyanidins were isolated and denominated geraniins A (6) and B (6a). Later, in 2001, geraniins C (7) and D (7a) (Calzada et al, 1999) were found. A recent study reported that geraniin A possesses antioxidant activity (Adewusi and Afolayan, 2010).

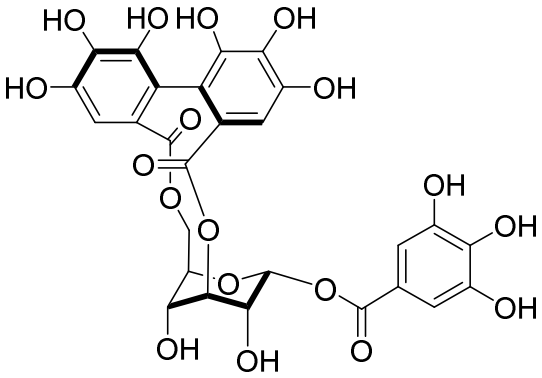


6 R, R1, R2 = H
6a: R, R2 = H; R1 = OH
geranin A (6) and B (6a)



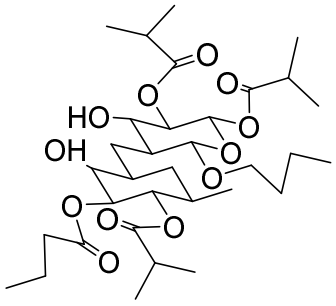
7: R, R1, R2 = H
7a: R, R2 = H; R1=OH
Geranina C (7), geranina D (7a)

Geranium pusillum, commonly known as the small-flowered cranesbill or (in North America) the small *geranium*, contains 1-O-galloyl-3,6-hexahydroxybiphenyl-D-galactopyranoside (pusilagin, 8), a polyphenolic compound extracted from the plant's aerial parts (Kobakhidza and Alaniya, 2004). The aqueous ethanolic extract of *Geranium wallichianum* showed antibacterial activity against *Staphylococcus aureus* (Ahmad et al, 2003), and the study of the chemical constituents of the whole plant resulted in the isolation and characterization of six compounds. These six compounds were identified as ursolic acid, β-sitosterol, stigmasterol, β-sitosterol galactoside, herniarin, and 2, 4, 6-trihydroxyethylbenzoate, which were isolated for the first time from *Geranium wallichianum* (Mohammad et al, 2009).



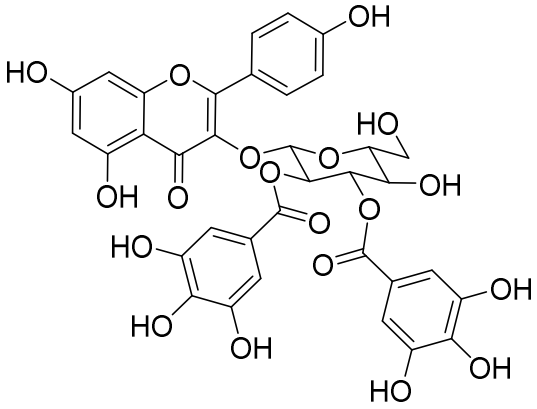
Pusilagin (8)

Geranium caespitosum produces neohesperidoside (9), which is able to potentiate the action of drugs such as ciprofloxacin, norfloxacin and berberine by 10-100 times against bacteria such as *S. aureus*, *S. aureus* NorA, *Bacillus subtilis*, and *Bacillus megaterium* (Oshiro et al, 2004). Additionally, *Geranium carolinianum L.* is commonly used in traditional Chinese medicine (TCM) and is effective for eliminating wind damp and treating diarrhea. It is clinically used to treat arthralgia due to wind damp, anesthetization, and muscle constriction. It has been reported that *Geranium carolinianum* L., as well as the majority of the congeneric plants, contain significant amounts of tannins, flavonoids, organic acids, and volatile oils (Pharmacopoeia of the People´s Republic of China, 2010). In addition, it has been shown that their roots contain a substance that can be extracted with water and represents a biological mechanism to control bacteria (*Ralstonia solanacearum*) that attack potatoes (Ercil et al, 2005).

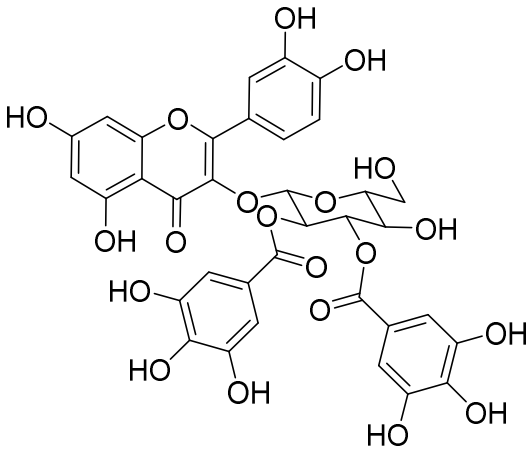


Neohesperidoside (9)

From *Geranium pyrenaicum*, which exhibits antileishmanial activity (Calzada et al, 2005), a new glycosylate flavonoid, 3-O-(2", 3"-di-O-galloyl)-O-D-glucopyranoside of kaempferol (10), was isolated, as well as an uncommon quercetin derivative, 3-O-(2", 3"-di-O-galloyl)-O-D-glucopyranoside of quercetin (10a). From the roots of *Geranium mexicanum*, the compounds with the most antiprotozoal activity were flavan-3-ol-(-)-epicatechin (showing moderate activity), (+)-catechin, tyramine, and 3-O-β-D-glucopyranoside of β-sitosterol.

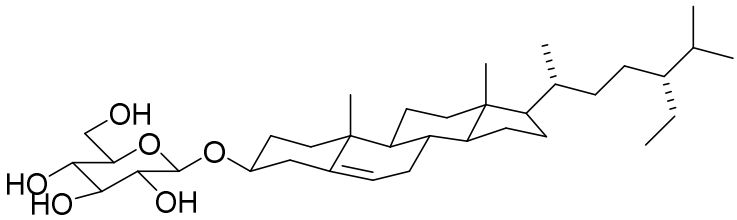


Kaempferol 3-*O*-(2”,3”-di-*O*-galoil)-β-D-glucopiranóside (10)

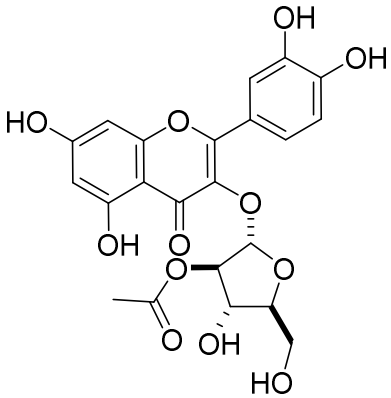


Quercetin 3-*O*-(2”,3”-di-*O*-galoil)-β-D-glucopiranóside (10a)

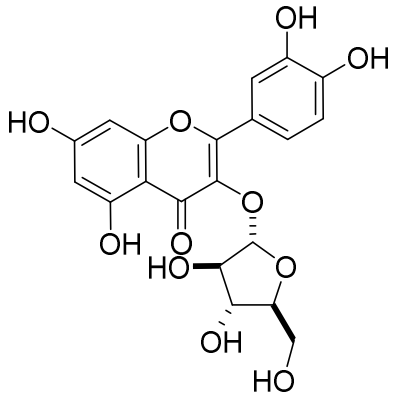
Geranium bellum Rose, which was studied by our group (Gayosso-De-Lucio et al, 2010; Vazquez-Gónzález et al, 2014), is a perennial plant with long roots that is found in the grassy meadows bordering pine/oak forests in the mountains of Hidalgo State, Mexico, where it is known by its popular name, “*pata de león*”. It has been used as a traditional remedy for fever, pain, and gastrointestinal disorders. Radical scavenging assay-guided fractionation of the antioxidants from MeOH and EtOAc extracts of the aerial parts of *Geranium bellum* resulted in the isolation of β-sitosterol 3-O-b-D-glucopyranoside (11), quercetin 3-O-a-L-(2”-O-acetyl) arabinofuranoside (12), quercetin 3-O-a-L-arabinofuranoside (avicularine) (13), quercetin, methyl gallate, gallic acid, methyl brevifolincarboxylate, and dehydrochebulic acid trimethyl ester. The antioxidant activity of the extracts (both initial fractions and pure compounds) was tested by measuring their capacity to scavenge 2, 2’-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radicals; this technique is a widely employed assay for screening natural products for antioxidant activity.



β-sitosterol 3-O-b-D-glucopyranoside (11)



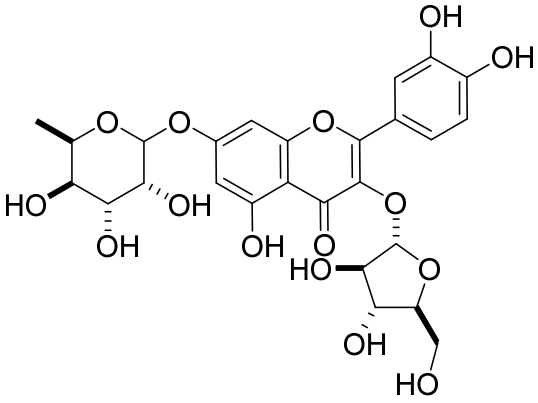
Quercetin 3-O-a-L-(2”-O-acetyl) arabinofuranoside (12)



Quercetin 3-O-a-L-arabinofuranoside (avicularine) (13).

Constituents from the aerial parts of *Geranium potentillaefoium* found in certain studies included geraniin, corilagin, gallic acid, methyl gallate, methyl brevifolincarboxylate, quercetin, quercetin 3-O-β-D-glucopyranoside, quercetin 3-O-β-D-[6"-O-galloyl) glucopyranoside, kaempferol, β-sitosterol 3-O-β-D-glucopyranoside, and β-sitosterol (Shim et al, 2009).

Another *geranium* studied by our group is *Geranium Shiedeanum* (Gs). The phytochemical study of Gs led to the isolation of the following hydrolyzable tannins, which are well known as potent antioxidants: gallic acid, geraniin, ellagic acid, and a lesser proportion of the kaempferol glycoside flavonoid, 3-O-α-L-arabinofuranoside-7-O-β-D-rhamnoside of kaempferol (14). Notably, to our knowledge, this is the first time these compounds have been identified in this genus. In addition, the yield of geraniin in the crude extract was 40% (Gayosso-De-Lucio et al, 2014; Madrigal-Santillán et al, 2015).



Kaemphferol 3-O-α-L-arabinofuranoside-7-O-β-D-rhamnoside (14).

Geranium sibiricum Linne (GSL), a widespread herb, has been used for treating diarrhea and intestinal inflammation in Korean traditional folk medicine. EtOH extracts of GSL (EGS) inhibit the expression of various kinases and nuclear transcription factors involving nuclear factor (NF)-κB, activator protein (AP)-1, COX-2 and iNOS. These findings indicate that treatment with EGS decreased gene expression of interleukin (IL)-1β and COX-2 in PMACI stimulates HMC-1 cells.

Conclusion

It has been observed that natural hepatoprotective drugs have fewer side effects or less interaction as compared with allopathic medicines, but natural products require more scientific evidence to evaluate their safety and effectiveness. Also, studies of traditional hepatoprotective medicinal products are limited and further study of products and practices is needed. Pharmacokinetic and toxicity studies have not disclosed any issues that could limit the therapeutic use of these extracts. Also, additional study is required in order to identify glycosides, flavonoids, triterpenes, and phenolic compounds as classes of compounds with hepatoprotective activity. Further studies including clinical trials need to be conducted to ascertain the safety of these compounds as good alternatives to conventional drugs in the treatment of liver diseases.

In the *Geranium* genus, different flavonoids and phenolic compounds with higher antioxidant power have been identified, and their main component is geraniin. This substance, isolated from *Geranium thunbergii*, has been evaluated and it demonstrated antihypertensive activity biologically, inhibiting the angiotensin converting enzyme and the reverse transcriptase of RNA tumor viruses; immunomodulatory activity has also

been found in the plant as well. On the other hand, kaemferol, another compound found in *geraniums*, has been described as a flavonoid with antioxidant power. These and other compounds found in some *Geranium* species lead us to think that this is a genus from which promising results can be obtained in relation to ethanol-induced hepatotoxicity. Table 1 is a summary of genus, active compounds, and beneficial effects of *Geranium*.

Table 1: Genus, active compounds, and beneficial effects

Botanical Name	Main active compounds	Beneficial effects
Geranium macrorrhizum	Germacrone	Precursor of pheromones, hepatoprotective action against CCl4-induced liver damage and strong antibacterial activity. Immunostimulatory properties.
Geranium robertianum L.	Hyperoside, ellagic acid, isoquercitrin, quercitrin, kaempferol, caftaric acid, and rutoside	Increased diuresis, exerted anti-hyperglycemic effects, increased the coupling effectiveness between the oxidative and phosphorylative systems.
Geranium sylvaticum	Malvidin	Strong antioxidant activity. Will be subjected to further investigations.
Geranium sanguineum L.	High polyphenolic complex (tannins, flavonoids and catechins)	Significant inhibitory activity against the influenza virus and herpes simplex, traditionally used for treatment of skin lesions and for the relief of pruritus and itching and gastrointestinal disorders.
Geranium pratense	Myricetin, tryptophan	Inhibited the action of the amylase enzyme in mouse plasma, traditionally used as anti-diarrheic, diuretic, tonic, hemostatic, stomachic and anti-diabetic drug.
Geranium niveum	Proanthocyanidins and other phenolics compounds	Anti-inflammatory, antiviral, antibacterial, enzyme-inhibiting, antioxidant and radical-scavenging properties.
Geranium pusillum	Pusilagin	Antioxidant activity.
Geranium wallichianum	Ursolic acid, β-sitosterol, stigmasterol, β-sitosterol galactoside, herniarin	Antibacterial, antifungal, cytotoxic, phytotoxic, insecticidal and enzyme inhibitory activities.
Geranium caespitosum	Neohesperidoside	Potentiate, by 10 to 100 times, the action of drugs such as ciprofloxacin, norfloxacin and berberine, against bacteria such as *S. aureus*, *S. aureus* NorA, Bacillus subtilis and Bacillus megaterium.
Geranium carolinianum L.	Tannins, flavonoids, organic acids, and volatile oils	Traditionally used to treat diarrhea. It is clinically used to treat arthralgia due to wind damp, anesthetization, and muscle constriction.
Geranium pyrenaicum	ellagitannins corilagin tellimagrandin I	Antileishmanial activity.
Geranium mexicanum	flavan-3-ol-(-)-epicatechin, tyramine	Antiprotozoal activity.
Geranium bellum Rose	quercetin, methyl gallate, gallic acid, methyl brevifolincarboxylate, and the dehydrochebulic acid trimethyl ester	Inactivate triosephosphate isomerase from *Trypanosoma cruzi*, traditional used as treatment of fever, pain, and gastrointestinal disorders.
Geranium potentillaefoium	geraniin, corilagin, gallic acid, methyl gallate, methyl brevifolincarboxylate, quercetin, quercetin 3-O-β-D-glucopyranoside	Strong antioxidant activity. Will be subjected to further investigations.
Geranium Shiedeanum	gallic acid, geraniin, ellagic acid, kaempferol glycoside flavonoid	Hepatoprotective effects. Traditionally used for treatment of fever, pain, and gastrointestinal disorders.
Geranium sibiricum Linne	corilagin and geraniin	Action against intestinal inflammation, dermatitis, and diarrhea.

Acknowledgments

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