Chemické Listy

Review

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ON BITTER GENTIAN AND BITTER GENTIANELLA

Michal Jurášek and Pavel Drašar

Institute of Chemistry of Natural Substances, University of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic
drasarp@vscht.cz

The article provides basic information about biologically active substances from gentians in traditional and contemporary healing practice and about the use of gentian in Eastern medicine, and also provides information about the intensity of bitterness of some of the compounds contained.

Keywords: gentian, dwarf gentian, *gentiana*, *gentianella*, TCM, ayurveda

Gentiana Linn. is the largest genus in the Gentianaceae family and includes more than 360 species, including the“extinct“and later“non-native“yellow gentian in Bohemia and Slovakia[1]. (*Gentiana lutea* L., also gelber Enzian), which is an important representative of gentian among medicinal herbs, as well as some Asian species. Its root is used in pharmacy (the official drug is listed in the European Pharmacopoeia Ph. Eur. 11. (ref.[2]) under the name *Radix gentianae, Gentianae tincture is also listed there,* and even in the Czech Pharmacopoeia 1997, ref.[3]). It is traditionally used in herbal medicine for digestive disorders. It suppresses dyspeptic symptoms in disorders of the gallbladder, liver and pancreas. It supports blood formation, central nervous system function and can be used as a general tonic during convalescence after serious illnesses. Externally, the drug can be used on non-healing and swollen wounds. It has even been indicated for cows to improve milk quality[4].

As Všemír Berchtold says[5]: “*Gméno, české nosj pro hořkost swau; latinské ale má na památku Gentiana krále illirského čili slowanského*“ (“*The Czech name has for its bitterness; the Latin in memory of Gentiana, the Illyrian i.e. Slavonic king*”) (Correctly Gentios (Greek: Γένθιος, Albanian: Genti) was an Illyrian king from the Labeatae tribe. He ruled in the years 181–168 BC, and is said to have discovered the beneficial effects of gentian[6]).

The oldest university document, known to the authors, describing gentian is the doctoral dissertation of Weber Johann Andreas from 1720 from the University of Jena, which nevertheless relies on all the classics, such as Dioscorides, Pliny, Galen, Matthioli and others. This work already dealt with the fact that the then known literature was not very precise in identifying plants and contained many different names for one plant, and conversely one name for different plants. In the past, some taxonomists also combined the genera *Gentianella* (dwarf gentian) and

Fig. 1. **Gentian (yellow)[7], dwarf gentian[8], gentian (blue)[9]**

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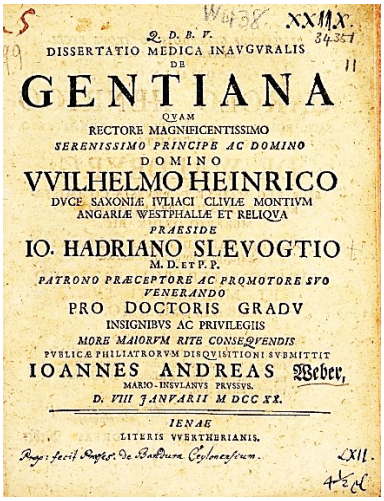
Q. D. B. V.
DISSERTATIO MEDICA INAVGVRALIS
DE
GENTIANA
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DOMINO
VVILHELMO HEINRICO
DVCE SAXONIÆ IVLIACI CLIVIÆ MONTIVM
ANGARIÆ WESTPHALIÆ ET RELIQVA
PRÆSIDE
IO. HADRIANO SLEVOGTIO
M. D. ET P. P.
PATRONO PRÆCEPTORE AC PROMOTORE SVO
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MARIO-INSVLANVS PRVSSVS.
D. VIII IANVARII M DCC XX.
IENAE
LITERIS VVERTHERIANIS.

Fig. 2. **Frontispiece of Weber's dissertation**

Fig. 3. **Horec juniper brandy and Horec vodka (Prelika, a.s. Prešov)**

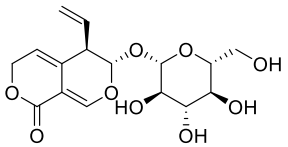
Gentiana (gentian), but in current taxonomy they are classified in different subtribes and are not directly related[10].

Tourists certainly remember mountain lodges in Slovakia, where almost everywhere at the bar counter they came across a five-liter pickle jar full of gentian roots and covered with juniper brandy[11] or other spirits. This elixir, called "koreňovica", refreshed and, as written above, healed the tourist in body and soul. The root was used to produce spirits even after fermentation[12], not only after maceration[13]. Gentian root is a frequent component of bitter alcoholic specialties, such as vermouths, aperitifs, liqueurs (Jägermeister), amarettos (Fernet-Branca), or "bitters"(Angostura bitters)[14]. As Presl writes[15]: "*Dělají z něho nápoj líhový i ohořčují jím kořalky a rosolky. Též jej dáwají do piwa na místo chmele.*" ("*They make an alcoholic beverage out of it and use it to bitter spirits and liqueurs. They also put it in beer instead of hops.*") Some time ago, in this journal, we even brought the original recipe for making Becherovka according to Johan Becher from 1866, where the root of the gentian is one of the main ingredients[16].

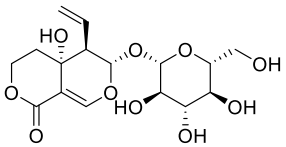
In today's Slovakia, you can get borovička (juniper brandy) and vodka (and many other specialties) flavored with bitter gentian root extract. It is all the more interesting that gentiopikrosid contained in gentian can be used in the treatment of alcoholic hepatosteatosis (fatty liver disease[17,18]).

The main components of the pharmacopoeial[3] raw materials (*Radix gentianae*; dried fragments of gentian roots and rhizomes) are bitter* secoiridoids gentiopicroside (gentiopicrin ; 2–8%, sometimes up to almost 10%), sweroside (0.05–0.08%)), amarogentin (0.01–0.08%), swertiamarin (swertiamaroside, swertimarin) and related amaropanin and amaroswerin, deglucosyltrifluoroside and desacetylcentapicrin.

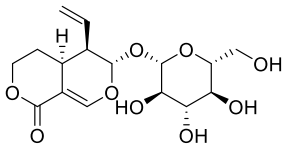
Apparently the leading compounds in inducing the sensation of bitterness are amarogentin[19] (bitterness 58,000,000, ref.[20]) and amaroswerin (bitterness 58,000,000, ref.[21]); further contributors to bitterness are



gentiopicroside

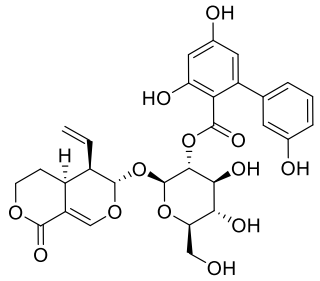


swertiamarin

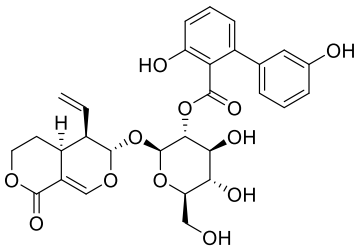


sweroside

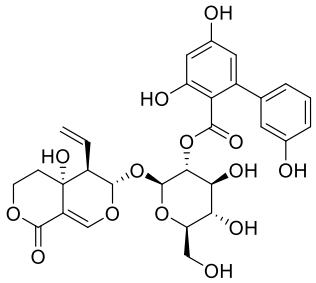
* Bitterness is usually determined by comparing the bitterness of a substance with a known standard, often quinine hydrochloride (bitterness 200,000), and is expressed as the reciprocal dilution that still produces a detectable bitter taste (EDQM. European Pharmacopoeia, 10th ed.; EDQM: Strasbourg, France, 2019). A bitterness value of 1000 means that 1 g of the substance or extract of 1 g of the drug in 1000 ml of water still tastes bitter. Bitterness in this sense is not identical to the IBU or EBU values for beer (Verhoef B.: Velká encyklopedie piva, Rebo, Čestlice 2003).



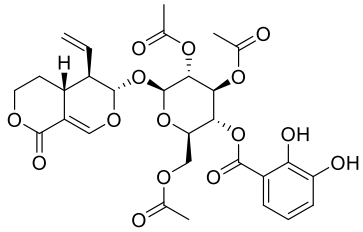
amarogentin



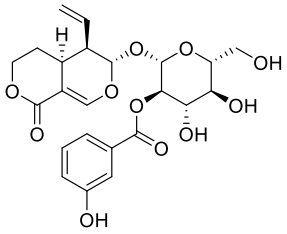
amaropanin



amaroswerin

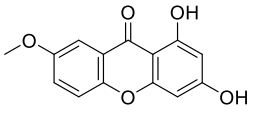


deglucosyltrifluoroside

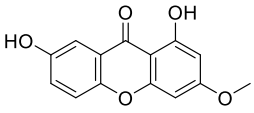


desacetylcentapicrin

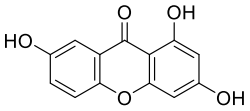
amaropanin (bitterness 20,000,000, ref.[21]), desacetylcentapicrin (bitterness ca. 4,000,000, ref.[22]) , secoiridoids gentiopicrin (bitterness 12,000, ref.[23]) and sweroside (bitterness ca. 12,000, ref.[20]). The most abundant bitter component, gentiopicroside (bitterness 11 600), has a real possibility of contributing to the treatment of various diseases, including digestive tract disorders, malignant changes, neurological disorders, microbial infections, bone formation disorders, inflammatory conditions and others[24].



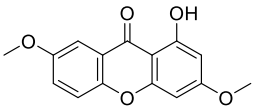
isogentisin



gentisin



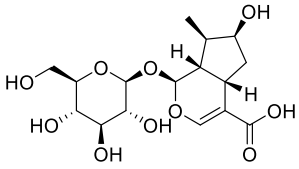
gentisein



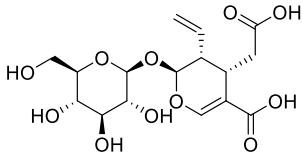
1-hydroxy-3,7-dimethoxyxanthone

Other components include xanthones (up to 0.1%), such as gentisin (gentianic acid, gentianin), isogentisin, methylgentisin (a series, especially medical and pharmaceutical sources, describe this substance by name, but do not say which of the two hydroxy groups of gentisine is methylated, SciFinder does not register such a trivial name, the only searchable citation[25] does not mention the substance or structure), gentisine and 1-hydroxy-3,7-dimethoxyxanthone.

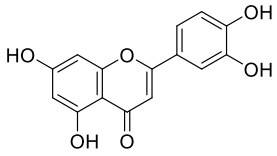
Another larger group are the iridoids, loganic acid (loganinic) and secologanoside.



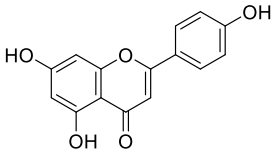
loganic acid



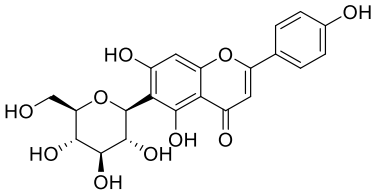
secologanoside



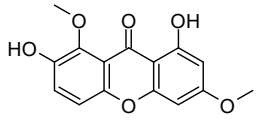
luteolin



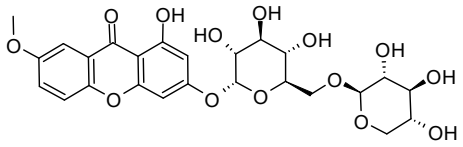
apigenin



isovitexin



gentiakaulein



gentioside

Flavonoids such as luteolin (cyanidenone, digitoflavone, flacitran, luteolol, Weld lake, Yama Kariyasu), apigenin, isovitexin (homovitexin, apigenin-6--*C*-β-D-glucoside, avroside, isoavroside, saponaretin), phytosterols and essential oil (0.1–0.2%) are also present.

Dried roots contain 30–55% carbohydrates, such as monosaccharides (D-glucose and D-fructose), disaccharides (sucrose and gentiobiose), trisaccharides (gentianose – 2.5–8.0%) and polysaccharides (pectins).

Pharmacopoeial quality gentian root must have a bitterness value of at least 10,000 and must also contain at least 33% water-soluble extract (European Pharmacopoeia 2010)[26].

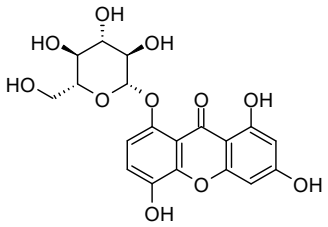
Classical Ayurveda uses the rhizome of Himalayan *Gentian kurroo* Royle[17] (Indian or Himalayan gentian, trāyamāṇa, त्रायमाण), which contains mainly gentisin, swertiamarin, gentiopicroside (main component), amarogentin, sweroside, substances contained in our *Radix gentianae.* As substances specific to trāyamāṇa (which are also found in other drugs), we can name gentiakaulein (gentiakaulen), gentioside, norswertianolin (demethylbellidifolin-8-*O*-glucoside), mangiferin[27].

Ayurveda uses trāyamāṇa as a cooling (śīta) and sweet (madhura) principle, relieving gulma (false abdominal lumps caused by bloating, or rather an imbalance of the three doshas (vata, pitta and kapha)), fevers, impaired kapha (which mainly affects body fluids, skeletal and muscular structure) and blood disorders. It treats dizziness, thirst, tuberculosis, exhaustion, poisoning and vomiting[28].

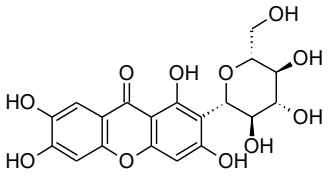
Traditional Chinese medicine[29] uses the rhizome of gentian (*Gentianae macrophyllae radix,* GMR, qin jiao, 秦艽) as a middle-class traditional Chinese drug with the effects of dispelling wind-induced dampness, clearing damp-heat, reducing heat deficiency and relieving pain. It has been used to treat joint pain, stroke, childhood fever and damp-heat jaundice, etc. The 2020 edition of the Chinese Pharmacopoeia states[30] that GMR is the dried root *of Gentiana macrophylla* Pall. (with synonyms *of Gentiana straminea* Maxim., *Gentiana crassi-caulis* Duthie ex Burk. or *Gentiana dahurica* Fisch). Liu et al.[29] report 191 chemical compounds in GMR, the main ones of which are listed above (gentiopicroside is again listed as the main constituent). We see here, among others, 12 iridoids, 50 secoiridoids, 8 polymeric iridioids, 5 triterpenoids of oleanane and ursane type, 12 flavonoids, 7 steroids, 5 alkaloids, mainly containing a pyridine nucleus, lignans, sesquiterpenes and phenylpropanoids.

Modern pharmacological studies have shown that the pharmacological activity of GMR is mainly manifested by anti-inflammatory effects. It also has other activities, such as antitumor, hepatoprotective, immunoregulatory and cardiostimulatory.

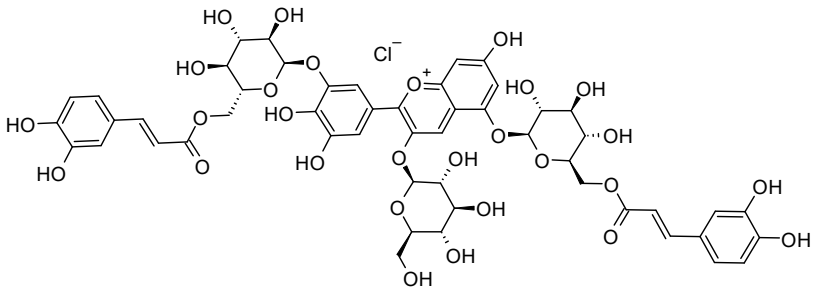
The beautiful blue color of the petals of most gentians is based on the characteristic spectral absorption



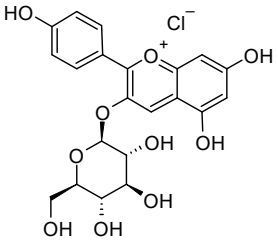
norswertianolin



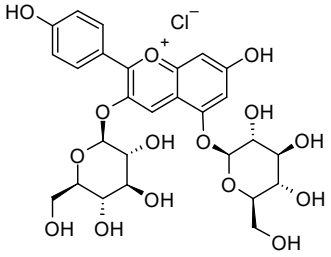
magniferin



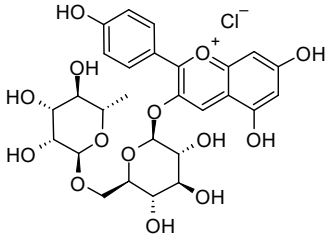
gentiodolphin



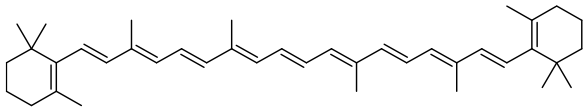
pelargonidin-3-*O*-glucoside



pelargonidin-3,5-*O*-diglucoside



pelargonidin-3-*O*-rutinoside



β-carotene

of a stable anthocyanin, gentiodelphin[31], with the lovely systematic name 5-6-*O*-(2*E)*-3-(3,4-dihydroxyphenyl)-1--oxo-2-propen-1-yl-β-D-glucopyranosyloxy-2-3-6-*O*-(2*E)*-3-(3,4-dihydroxyphenyl)-1-oxo-2-propen-1-yl-β-D-glucopyranosyloxy-4,5-dihydroxyphenyl-3-(β-D-glucopyranosyloxy)-7-hydroxy-1-benzopyrylium chloride, which was isolated from the aforementioned petals in a yield of 0.01% (ref.[32]).

The yellow to orange color of *G. lutea* is due to carotenoids[33], especially β-carotene, and the orange tone *of G. lutea* L. var. *aurantiaca* is due to anthocyanins, such as pelargonidin-3-*O*-glucoside, pelargonidin-3,5-*O*-diglucoside (pelargonin) and pelargonidin-3-*O*-rutinoside[34], of course in the form of salts.

Gentian and its "relatives" represent not only the beauty of nature, but also the healing power that nature has wisely placed in magical herbs so that wise people can benefit and enjoy them.

The article is part of a series of contributions describing various chemical aspects of the issue of natural substances, such as[35–38].

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