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## Medicinal, biological and phytochemical properties of Gentiana species

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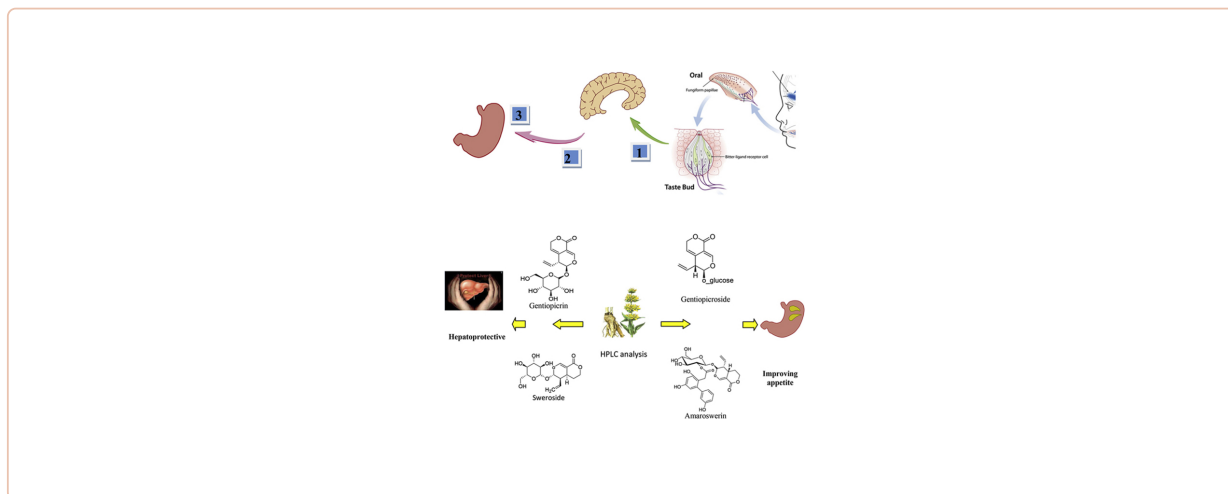
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### Abstract

Gentiana, a cosmopolitan and important genus of the Gentianaceae family, comprises 400 species distributed among the world. Based on the studies of Iranian traditional medicine texts, there are some promising bioactivities for this genus that is unknown in modern medicine and some of them are still the basis of new remedies. In traditional medicine texts, Gentiana's different exclusive forms of preparations are effective for treatment of some disorders such as menstrual over-bleeding, conjunctivitis, vitiligo, animals venom poisoning, injuries, infected wounds, pain and swelling of liver, spleen, stomach and sprains of muscles. There are some activities that are the same in traditional and modern medicine such as anti-inflammatory, hepatoprotective and diuretic effects. Phytochemical investigations on the title genus have led to characterization many secondary metabolites. Secoiridoidal and iridoid glycosides such as gentiopicroside, xanthones, monoterpene alkaloid; polyphenol and flavones are the constituents that have been shown the pharmacological activities in different gentian species. This article studies the Gentiana according to the Iranian traditional and modern medicine.

**Keywords:** Gentiana, Gentianaceae, Iranian traditional medicine, Anti-inflammatory, Gentiopicroside

### Graphical abstract



## 1. Introduction

The use of medicinal plant goes back to the beginning of human life on earth, exploiting the plants of their natural surroundings. Looking to natural products for bioactive compounds and new drug discovery is considerable nowadays. Researchers have thus turned to traditional medicine, which is still used widely throughout the world. Traditional medicine consists of a lot of valuable practical information in conjunction with the therapeutic principles and using materials including herbs, animal parts and inorganic materials as therapeutic agent.<sup>1</sup> The role of Iranian and Muslim physicians in the development and progress of medicine is significant and is highlighted in the evolution of medicine. Al-Razi (Fig. 1) and Avicenna were the two famous Persian philosophers and physicians that owning different medical masterpieces such as *Al-Hawi* (Fig. 2) and *Al-Qanun*. The contents of the mentioned books are based on their own observations and their scientific experiments. These texts established the basis of medical theory and they were comprehensive sources which guided scholars in the past decades.<sup>2</sup>

The name Gentian is derived from the name of a king who was first identified the plant or healed by it, his name was Gentius.<sup>3</sup> Dioscorides (the Greek physician) believed that the king Gentius was identified the properties of this plant and used the plant root in 167 BC by the incidence of Plague.<sup>4</sup> Based on the studies of the traditional medicine texts, the name *Gentiana* is related to the genus of the plant and this name covers all of its species.<sup>5</sup>

Gentianaceae are the third largest family of Gentianales, with Apocynaceae and particularly Rubiaceae being considerably more species-rich. Gentianaceae includes 1700 species in 91 genera with a great diversity of habitats, morphology and ecology.<sup>6</sup> *Gentiana* is the largest genus of Gentianaceae family with more than 400 species.<sup>7</sup> Numerous species within Gentianaceae family have ornamental value, especially the species belonging to the *Gentiana* genus, and also present pharmaceutical interest due to its interesting phytochemical properties.<sup>8</sup> In many developing countries, medicinal plants have not been well studied, tested or documented.<sup>9</sup> The objective of this work was to elicit data on the traditional and modern uses of *Gentiana* as a medicinal plant. In addition, the present paper provides baseline data for future pharmacological and phytochemical studies.

## 2. Botanical aspects

### 2.1. Morphology

The life forms of Gentianaceae are so different and it depends on their inhabitation. In the mid-latitudes and mountains, annual and perennial grasses are growing, whereas in the subtropical and tropical areas shrubs, sub-shrubs, lianas and small trees can also be found.<sup>10</sup> In this family, stems are ascending, erect, or twining. Leaves are opposite, less often alternate or whorled, simple, base connate; stipules absent. Fruit a 2-valved capsule, rarely a berry. Seeds are many or rarely few, small; endosperm abundant.<sup>11</sup> Flowers are bisexual, hypogynous, 4- or 5-merous, or rarely zygomorphic. Inflorescences are terminal or axillary, and

are usually cymose, but less often racemose, capitate, clustered or spicate. Members of the family do not produce latex and stipules are absent.<sup>12</sup> The pattern of Gentian family and some *Gentiana* species are shown in Fig. 3, Fig. 4.<sup>13</sup>

## 2.2. Distribution

Distributions of Gentianaceae family are mainly in temperate zones and highland regions except for a few that can be found in the tropics.<sup>6</sup> The center of diversity of Gentianaceae is situated in Himalaya and subalpine or alpine region.<sup>14</sup> Different species have spread from Europe to Asia. There are some species which are distributed throughout the south and central European high mountains such as *Gentiana acaulis*, *Gentiana alpine*, *Gentiana angustifolia*, *Gentiana clusii* and some other species are widespread from the Alps, Pyrenees to Carpathians high mountains.<sup>15</sup> The Tibetan Plateau in central Asia is endemic for different *Gentiana* species such as *Gentiana dahurica*, *Gentiana straminea*, *Gentiana crassicaulis*, *Gentiana robusta*, *Gentiana siphonantha*, *G. dendrologi*, *Gentiana waltonii*, *Gentiana tibetica*, *Gentiana lhasica*, and *Gentiana officinalis*.<sup>16</sup> *Gentiana kurro* is endemic to the northwestern Himalayas and commonly grows in Kashmir.<sup>17</sup> A series of species have dispersed in some areas of Iran: *Gentiana caucasica*, *Gentiana gelida* and *Gentiana septemfida* in northern and north western highlands,<sup>18</sup> and *Gentiana olivieri* is commonly seen in flat zones toward hillsides and in low slopes of southwestern highlands.<sup>19, 20</sup> Location of some *Gentiana* spp. is shown in the world map (Fig. 5).

## 2.3. Collection & storage

The root and rhizomes of 4–6 years old plant (in order to obtain economically acceptable yields), are collected in autumn, when the flowers disappear and the leaves go brown. They divided into small parts for washing and then dried in 60–65 °C. For the preparation of alcoholic beverages, the fresh roots can be prepared for the market.<sup>21, 22</sup>

## 3. *Gentiana* in Iranian traditional medicine

### 3.1. Temperament of *Gentiana* in traditional medicine (Intrinsic characteristic)

From the perspective of Iranian traditional medicine, the nature of all beings, including inanimate objects, plants and animals is formed by the nature of the four elements: earth, water, air and fire. These elements are called quadruplet pillars. Each of these elements has a special quality. By the action and reaction of these four elements, some qualities will be dominant in objects which are called temperament or nature. Fire is warm and dry, air is warm and wet, water is cold and wet, and soil is cold and dry. These four elements are responsible for some characteristics in things. Soil making stability and shaping, water is responsible for flexibility and formability, air increases lightness and porosity and fire increases mobility of things. The differences between all beings are due to differences in the amount and proportion of these quadruple pillars.<sup>23</sup> Medicines are graded into four degrees with different properties as follows: the first degree is a low dose of medicine which does not produce any dominant quality in the body but more and repeated doses will make minor changes in body's quality. Second degree is a low dose of medicine that produces a dominant quality in the body, and more and repeated doses of it will not cause any harm. Third degree of medicine produces a dominant quality in the body and more and repeated doses will harm the body but it will not be lethal and the forth degree of medicine is lethal. According to the literature available on Iranian traditional medicine, *Gentiana* is warm and dry in third degree.<sup>3, 24</sup>

### 3.2. Uses in Iranian traditional medicine

Based on the Iranian traditional medicine texts *Gentiana*'s species have different therapeutic properties which are related to the root of the plant. Treatment of urinary retention, menstrual, liver and spleen dysfunctions and detoxifying of animal poisons are the main and common properties among the texts.<sup>3, 24, 25</sup> Drinking the *Gentiana* extraction prepared by macerating grinded root in water was beneficial for treatment of inflammation and swelling of liver, spleen, stomach, muscle weakness and sprains, and also for treatment of amenorrhea and urinary retention. The plaster of the root with vinegar was beneficial for bites of poisonous animals such as Scorpion and Pit viper, and also for healing injuries, inflammations and

infected wounds, it was also used for treatment of vitiligo. The amount of 4.64 g of *Gentiana* root with pepper and *Ruta graveolens* was an antidote for poisonous animal venoms. It was recommended that *Gentiana* is one the most potent antidote for scorpion, snakes and pit viper bites or unintentionally toxins drinking. For cessation of menstruation over bleeding, the *Tela* of *Gentiana* root and *Lawsonia inermis* leaf on palm was beneficial but the *Lotokh* of the root was used for treatment of conjunctivitis. *Tela* and *Lotokh* are the name of the most common preparations in ITM which the first one is refer to a low concentrated plant extraction pouring on the body surface but the latter is more concentrated. Drinking the squashed root with honey and lukewarm water and using the *Homul* of the root, caused abortion.<sup>3</sup> In ITM, *Homul* refer to vaginal or rectal suppository like preparation. In this form, the macerated plant extract is impregnated to a fabric then using as suppository. The proper dosage forms and preparations for the above disorders are mentioned in [Table 1](#).

#### 4. *Gentiana* in complementary medicine

Many countries in Africa, Asia and Latin America use traditional medicine to solve some of their primary health care needs. In industrialized countries, adaptations of traditional medicine are termed “Complementary” or “Alternative” Medicine. In Europe, North America and other industrialized regions, over 50% of the population have used complementary or alternative medicine at least once.<sup>27</sup> In many countries the uses of herbal medicine in combination with other therapeutic interventions for treatment of different diseases, is increased.<sup>28</sup>

A remarkable number of chronic hepatitis population patients are seeking helps from complementary and alternative medicine. Among the top 10 Chinese herbal formula prescribed for chronic hepatitis in Taiwan, Long-dan-xie-gan-tang which consists of *Gentiana scabra* and some other plants was the most common. The herbal drugs contained in this formula were reported to have multiple effects such as anti-virus, anti-inflammation, anti-oxidation or immune modulation.<sup>29</sup> In another study about managing hepatitis with alternative medicines, the high dose of a Chinese herbal preparation with the composition of 19 medicinal plant such as *Gentiana manshurica*, provides protection from hepatocyte necrosis in animal model.<sup>30</sup> According to the Avicenna, *Gentiana* is one of the medicinal plants that relive the hepatic obstruction. Drugs which possess property of astringent, diuresis and open obstruction such as *G. olivieri* and the others have been advised that they are strongly effective in liver diseases.<sup>31</sup> In some skin conditions complementary and alternative therapies are commonly used. Several Chinese herbal medicine formulas is using for treatment of vitiligo. Among these formulas Zi-ni-bai-ling-fang consists of *G. scabra* and the other plants. There is a superior effectiveness in those receiving oral herbal medicine plus narrow-band ultraviolet B (NB-UVB) when compared to phototherapy alone.<sup>32</sup> The number of patients with severe atopic dermatitis was under treatment with herbal medicine. Decoction of plant material such as *Gentiana* and the others were effective for reducing erythema, pruritus and exudates in atopic dermatitis.<sup>33, 34</sup>

##### 4.1. Substitute (Allied drug) in Iranian traditional medicine

There are some medicinal plants that can be used instead of *Gentiana*: one and a half time *Asarum europaeum*, half time root bark of *Capparis spinosa* and equal amount of *Aristolochia*.<sup>3, 24, 25</sup>

##### 4.2. Adverse reactions and its treatment in Iranian traditional medicine

*Gentiana* is harmful for lung and is contraindicated in pregnant women due to occurrence of abortion. *Asplenium scolopendrium* up to 4.64 g is an alternative for *Gentiana* in case of lung dysfunctions.<sup>3</sup>

#### 5. *Gentiana* in other traditional medicine

Several species from the family Gentianaceae are used in traditional medicine of different countries. The number of *Swertia* plants which are belong to the Gentianaceae, are used in traditional medicine of India, China, Pakistan, Japan and other Asian countries in the treatment of liver disorders, anorexia, malarial and fever, diarrhea, dysentery and inflammatory diseases.<sup>35</sup> In Chinese traditional medicine different *Gentiana* species such as *G. dahurica*, *G. straminea*, *G. crassicaulis*, *G. robusta*, *G. siphonantha*, *Gentiana dendrology*, *G. waltonii*, *G. tibetica*, *G. lhassica* and *G. officinalis* are used for diseases related to hepatobiliary system disorders.<sup>16</sup> Long-dan-xie-gan-tang is the most commonly prescribed Chinese herbal

formula for chronic hepatitis which was recorded in ancient Chinese medicine as having inhibitive effects on inflammatory diseases of liver or gall bladder and other inflammatory conditions. *G. scabra* is one of the several herbal component in the above formula.<sup>29</sup> Root and leaves of *G. scabra* and *Gentiana macrophylla* has been used in Chinese herbalism for over 2000 years as an excellent tonic for digestive system, work on stomach, liver and gall bladder.<sup>36</sup> In Serbian traditional several species of Gentianaceae family such as *Gentiana lutea*, *Gentiana punctata* and *Centaurium erythraea* are used in the treatment of digestive disorders.<sup>37</sup> In traditional medicine of Italy, *G. lutea*'s macerated roots in alcohol were used as an external anti-rheumatic and anti-neuralgic remedies that should be rubbed on affected area.<sup>38</sup> The effectiveness of different *Gentiana*'s species in treatment of hepatic disorders and inflammatory diseases are significantly obvious in almost all of the traditional medicines. The recent investigation on the phytochemical constituents of Gentianaceae and specially the genus *Gentiana* has been showed that a mixture of secoiridoids and xanthenes are responsible for these activities.<sup>39, 40</sup>

## 6. Biological activity and phytochemistry of *Gentiana* species in modern medicine

Medicinal plants play an important role in the development of potent therapeutic agents. Many of herbal drugs came into use in the modern medicine through the uses of plant material in folklore or medicinal traditional systems.<sup>41</sup> According to some researches two-thirds of the world's plant species have medicinal potential value.<sup>42</sup> It is estimated that 10–100 million species or organisms living on earth. Higher plants contain 250,000–500,000 species that only 6% of them have been investigated for biological activities and 15% for their chemical constituents.<sup>43</sup> Surveys in China indicated that medicinal plants belong to 11,146 species from 2309 genera of 383 families, representing a rich biodiversity.<sup>44</sup> Plant belonging to genus *Gentiana* is very well-known for their pharmacological activities and different chemical constituents. Different *Gentiana*'s constituent (Fig. 8) with their activities is listed in Table 2.

Herbal products derived from *Gentiana* spp. roots, is very effective for improving appetite.<sup>20</sup> There are two pharmacological mechanisms by which bitter tastants impact digestion: (1) the cephalic-response model: this hypothesis is that the bitter substances pass to a special group of cells in the cerebral cortex and it stimulate the vagus nerve to both the salivary gland and the stomach (Fig. 6),<sup>53</sup> (2) the local-response model: bitter tastants act directly on the mucosa of the upper part of the gastrointestinal tract and especially on the bitter receptors to release of saliva and gastric juices.<sup>54</sup> The last hypothesis is supported by recent studies that bitter, sour, sweet and umami taste receptor cells are present in the stomach, duodenum, jejunum, ileum and colon of rats.<sup>55</sup> Secoiridoidal glycosides are the most important bitter constituents, belonging to *Gentiana* genus. Gentiopicroside, amarogentin, are the secoiridoids isolated from *G. lutea*'s root.<sup>45</sup> Secoiridoidal glycosides isolated from different *Gentiana* species have several important activities. Amarogentin and amaroswerin have the strongest gastroprotective effects among the other secoiridoids.<sup>46</sup> Gentiopicrocin and xanthone isogentisin, mangiferin from leaves and flowers of *G. lutea* have considerable antimicrobial activities.<sup>49</sup> The hepatoprotective activities are related to, sweroside, swertiamarin and gentiopicrocin, constituents of *Gentiana* root (Fig. 7).<sup>47</sup> A recent in vivo study shows that the methanolic extract of *G. manshurica* roots, has significantly reduced the increases in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and the serum and hepatic triglyceride levels in ethanol administered C57BL/6 mice and it also possessed the ability to prevent alcohol-induced acute liver steatosis by blocking CYP2E1-mediated free radical scavenging effects and sterol regulatory element-binding protein 1 (SREBP-1) synthesis. The last one is a hepatic sterol-regulatory element binding protein and a transcription factor regulating fatty acid and triglyceride (TG) synthesis which is activated in alcohol-treated mice.<sup>56, 57</sup> The anti-inflammatory and antitumor activities of several iridoid glycosides and flavonoids from the plant have also been proven recently. The root extract of *G. kurroo* exerted significant antioxidant activity as verified by DPPH, hydroxyl radical, lipid peroxidation and protective oxidative DNA damage assays. This activity is related to flavonoid content of the plant. The anti-proliferative property of *G. kurroo* root extract was determined by sulforhodamine B (SRB) assay against several cancer cell lines. The root extract inhibited cancer cell growth in cell line by inducing cell cycle arrest in Miapaca-2 cells at G0/G1 phase of the cell cycle and also by inducing a remarkable decrease in mitochondrial membrane.<sup>48</sup> Phytochemical studies on *Gentiana* species led to the discovery of other



compounds such as xanthenes, polyphenol and flavones which are responsible for cholinesterase inhibitory, antioxidant, antitumor and vascular smooth muscle cells (VSMC) proliferation inhibitory activities.<sup>50, 51, 58</sup> Gentianine is a monoterpene alkaloid which is widely distributed in several plant species of Gentianaceae family.<sup>59</sup> It is a crystalline alkaloid and an active metabolite of swertiamarin which have been reported to have diverse pharmacological activities. Antidiabetic effect of gentianine by regulating the gene expression of PPAR- $\gamma$ , GLUT-4 and adiponectin was recently proven.<sup>60</sup> It also possesses the other activities such as anti-inflammatory, antipyretic, sedative-hypnotic and diuretic effects.<sup>61, 62, 63, 64</sup>

## 7. Conclusion

Iranian traditional medicine is a comprehensive and dynamic source with the antiquity of thousands of years. Treatment of diseases and principle used are documented in many Iranian traditional texts. The fundamental of traditional medicine, etiology and treatment of diseases is based on, quadruplet pillars, the four elements in ITM. This has been established by temperaments.<sup>65</sup> Based on the Iranian traditional medicine texts, *Gentiana*'s different exclusive forms of preparations are effective in treatment of several disorders such as menstrual over-bleeding, conjunctivitis, vitiligo, animals venom poisoning, injuries, infected wounds, pain and swelling of liver, spleen, stomach and sprains of muscles. Such properties have not been reported and investigated so far except the healing effect on liver dysfunction and this might be a starting point for the development of the new therapeutic applications and more investigations on different *Gentiana*'s species in the future.

## Conflict of interest

The authors had no conflict of interest. The authors alone are responsible for the content and writing of the paper.

## Footnotes

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## Figures and Tables

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**Fig. 1**

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Avicenna.



**Fig. 2**

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The frontispiece of *Al-Hawi* by *Al-Razi* (Bodleian version).

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**Fig. 3**

Pattern of Gentianaceae.

**Fig. 4**

The number of *Gentia* species: (A: *G. dahurica*, B: *G. straminea*, C: *G. crassicaulis*, D: *G. robusta*, E: *G. siphonantha*, F: *G. dendrologi*, G: *G. waltonii*, H: *G. tibetica*, I: *G. lhassica*, J: *G. officinalis*).

**Fig. 5**

Location of *Gentiana* spp. is shown by red marks.



**Table 1**

The main uses of *Gentiana* in Iranian traditional medicine.

Organ systems	Disease	Part	Dosage	Preparation	Reference
Stomach	Pain and swelling	Root	4.64 g	Macerated <i>Gentiana</i> root in water	<a href="#">3</a>
Nerve-muscle	Muscle weakness and sprains	<b>Root</b>	<b>4.64 g</b>	<b>Macerated <i>Gentiana</i> root in water</b>	<a href="#">3</a> , <a href="#">26</a>
Liver and spleen	Inflammation and swelling	<b>Root</b>	6.68 g	<b>Macerated <i>Gentiana</i> root in water</b>	<a href="#">3</a> , <a href="#">25</a>
Skin	Vitiligo, injuries, infected wounds	Root	–	Plaster of the root with vinegar	<a href="#">3</a> , <a href="#">25</a>
Eye	Conjunctivitis	Root	–	Grinded root and <i>Lawsonia inermis</i> leaf macerated in water	<a href="#">3</a> , <a href="#">23</a>
Reproductive	Menstruation over bleeding	Root	–	Grinded root and <i>lowsonia inermis</i> leaf macerated in water	<a href="#">3</a> , <a href="#">26</a>
	Abortion	Root	2.23 g	Squashed root with honey and lukewarm water and the root's suppository	<a href="#">3</a> , <a href="#">26</a>

**Table 2**

*Gentiana*'s different constituent and activities.

<b>Gentiana species</b>	<b>Constituent classes</b>	<b>Constituent</b>	<b>Activities</b>	<b>Reference</b>
<i>G. lutea</i>	Secoiridoidal glycosides	Gentiopicroside (A), amarogentin (B), swertiamarin (C), amaroswerin (D)	Gastroprotective	<a href="#">45</a> , <a href="#">46</a>
<i>G. cruciata</i>	<b>Secoiridoidal glycosides</b>	Swertiamarin, gentiopicrosin(E)	Hepatoprotective	<a href="#">47</a>
<i>G. kurroo</i>	<b>Secoiridoidal glycosides</b>	Sweroside (F), swertiamarin, Gentiopicroside	Anti-inflammatory, antitumor	<a href="#">48</a>
<i>G. lutea</i>	Xanthones, secoiridoid glycosides	Isogentisin (G), mangiferin (H), gentiopicrosin	Antibacterial	<a href="#">49</a>
<i>G. kochiana</i>	Xanthones	Gentiakochianin (I), gentiacaulein (J)	Cytotoxic	<a href="#">50</a>
<i>G. lutea</i>	<b>Secoiridoidal glycosides</b>	Gentisin (K)	Vascular smooth muscle cells proliferation inhibitory	<a href="#">51</a>

**Fig. 6**

Cephalic phase (Neurogenic signals arise in the appetite centers of hypothalamus). 1: The taste or smell of food, tactile sensations of food in the mouth, or even thoughts of food cause stimulation in appetite brain center, 2: parasympathetic action potentials are carried by the vagus nerves to the stomach (pink arrow), 3: stimulation of enteric stomach nerves by vagus nerve and gastrin secretion.<sup>[52](#)</sup>

**Fig. 7**

Some of the activities relating to constituents of *Gentiana*.

**Fig. 8**

Chemical structures of *Gentiana* (A–K).

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