Anesth Crit Care 2019; 1 (1): 010-014 *DOI: 10.26502/acc.002*

Review Article

Natural Plant Compounds with Possible Interaction with Anesthetics

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Received: 29 April 2019; **Accepted:** 06 May 2019; **Published:** 13 May 2019

Abstract

The use of medicinal products is becoming more and more modern. Although little is known about the exact composition and effects of various herbal preparations, their plant and natural origin serve as evidence of their safety. The doctor is rarely notified of their use, while there is increasing body of evidence on the effects, side effects and interactions with synthetically produced drugs.

Keywords: Flavonoid; Drug; Herb; Anesthesia

1. Introduction

The use of herbal therapies is rapidly expanding in both developed and developing countries. These "natural" therapies are considered beneficial, but their adverse effects and potential interaction with other drugs are not evaluated [1]. Many currently used medicines originate from natural products, especially plants. Drugs and plants are closely linked to each other by traditional medicines or ethnomedicines. The history of herbal medicine is entangled with modern medicine. Many medicines listed as conventional medicines are originally derived from plants. Very well-known plant, the basis for salicylic acid and aspirin is white willow bark, precursor of quinine compounds is cinchona bark, the basis for digitalis is foxglove plant, and for example periwinkle provides the chemotherapeutic agent, vincristine. Morphine, which is derived from the opium poppy is the most widespread narcotic [2]. In the table 1 are listed some of drugs derived from plants, and are important and used in the perioperative period.

Drug	**Plant**
Morphine	*Papaver somniferum*
Atropine	*Atropa Belladona*
Digitalis	*Digitalis Purpurea*
Ephedrine	*Ephedra sinica*
Cocaine	*Erythroxylon coca*
Scopolamine	*Datura fastuosa*

Table 1: Common used drugs used in the perioperative period derived from plants (modified from [2]).

In recent years, many other potential herbal-derived therapeutic agents have been available. Plants and herbs are broad sources of not only drugs - medicines, but also of bioactive substances that could lead to the emergence of new drug structures.

2. Flavonoids

Flavonoids are the most common group of polyphenolic bioactive compounds which are present in the human diet and ubiquitously occur in edible and medicinal plants. Predominantly, are derived from vegetables and fruits, chocolate, beverages (tea, coffee, red wine) as well as from herbal preparations. Daily consumption of flavonoids ranges from tens of milligrams to over one gram [3]. The absorption and distribution of flavonoids is still not well understood, and their bioavailability is the center of interest [4].

Flavonoids are characterized by phenylbenzopyran chemical structure. They are structurally derived from the compound that includes C15 (C6–C3–C6), a tricyclic skeleton consisting of two aromatic rings and heterocyclic benzopyran ring. The fused aromatic ring is known as the A ring, phenyl constituent as the B ring and the benzopyran ring as the C ring. Flavonoids are divided into several subclasses according the type and number of substituents on C ring (Table 2) There is an abundance of natural flavonoids, with over 6000 different members of the flavonoid family reported [5, 6].

Flavonoid class	**Examples**
Flavones	Luteolin, Apigenin, Chrysin, Tangeretin
Flavanones	Hesperidin, Naringenin, Naringin, Eriodiktyol
Flavonols	Quercetin, Kaempferol, Myricetin, Rutin, Morin
Flavanols	Catechin, Epicatechin, Gallocatechin, Procyanidins, Prodelphinidins
Isoflavones	Daidzein, Genistein, Genistin, Daidzin, Glycitein
Anthocyanidins	Cyanidin, Delphinidin, Malvidin, Pellargonidin
Neoflavonoids	Calophyllolide

Table 2: Flavonoids classification.

2.1 (-)-Epigallocatechin gallate

(-)-Epigallocatechin gallate (EGCG), a flavanol constituent, catechin derivative present in green tea, the product of *Camellia sinensis* (Theaceae) is used for more than 4000 years in Chinese medicine for its powerful antioxidant properties. EGCG demonstrates dose-dependent anxiolytic, sedative–hypnotic and amnesic activity, with evidence that these activities are mediated at least in part by GABAA receptors [7, 8]. In the *in vitro* and *in vivo* experiments of Park et al. [9] EGCG in the dose 5-20 mg/kg prolonged the sleeping time of mice induced by pentobarbital. They suggested that EGCG anxiolytic and sedative effects are mediated by GABAA receptors [9].

2.2 Wogonin

Wogonin, is flavone isolated from *Scutellaria baicalensis* (Lamiaceae), an important traditional Chinese medical herb, with antibacterial and sedative properties. Study of Hui et al. [10] showed, that wogonin has the affinity for the benzodiazepine site of GABAA receptors in rat forebrain synaptosomal membranes. Park et al. [11] observed, that wogonin administrated i.p. in dose 10 mg/kg significantly block convulsions induced by pentylenetetrazole and electroshock but not strychnine.

2.3 Apigenin

Apigenin is flavone, which is present in the tea made from *Matricaria recutita*, Asteraceae family. It is used to treat stress, anxiety, insomnia and inflammation. Apigenin has the property of benzodiazepine partial agonist [5]. Plants of the genus *Passiflora* contain flavonoids with sedative properties, such as apigenin, chrysin and kaempferol. In the study of Gazola et al. [12] was evaluated the neurological effects of apigenin. Apigenin was administrated in the dose 0.6 mg/kg to sedate mice, and this effect was blocked with flumazenil (1 mg/kg). They suggest that apigenin modulates benzodiazepine site of GABAA receptors. In the study of Brown et al. [13] chrysin was administrated to rats in dose 2 mg/kg. Chrysin showed anxiolytic effect, which was affected by administration of flumazenil (3 mg/kg). Grundmann et al. [14] isolated kaempferol, flavonol from the ethanol extracts from leaves of *Apocynum venetum*. Their study showed, that kaempferol (0.02-1.0 mg/kg) exhibits anxiolytic effect on mice with the potency comparable to diazepam (1.5 mg/kg).

2.4 Amentoflavone

Amentoflavone is biflavonoid (*bis*-apigenin coupled at 8 and 3' positions, or 3′, 8″-biapigenin), it is pharmacologically active constituent of plants *Ginkgo biloba*, *Chamaecyparis obtusa* (hinoki), *Hypericum perforatum* (St. John's Wort). Amentoflavone exhibits diazepam-like affinity and is the most effective nitrogen-free benzodiazepine ligand. It was demonstrated that amentoflavone shows biphasic activity at nanomolar concentrations as a benzodiazepine antagonist and at higher concentrations as a flumazenil-insensitive negative modulator [3, 6, 15].

2.5 Kolaviron

Kolaviron, is a biflavonoid complex consisting of 3, 8-linked flavanone dimers such as GB-1 (Garcinia kola biflavonoid-1), GB-2 (Garcinia kola biflavonoid-2) and kolaflavanone, occurs predominantly in the seeds of *Garcinia kola* (Guttiferae). The fruits, seeds, nuts and bark of the plant have been used for centuries in folk medicine for the treatment of laryngitis, cough, fever and liver disease [16]. In the study of Tchimene et al. [17], was evaluated the local anesthetic activity of ethanol extracts from *Garcinia kola* seeds and their flavonoid components by an intradermal wheal assay using guinea pigs. According their results, GB-1 induced 92% local anesthesia at 10 mg/mL (i.d.), being comparable to the effect of lidocaine (0.66 mg/kg, i.d.).

3. Conclusion

Nowadays, the use of herbal medicine is very common, but the knowledge about the mechanism of action, metabolism of such preparations, and the clinical effects of many of the herbal preparations is still unknown. In many studies, there is growing evidence about drug side-effects and interactions of herbal drugs. There is also increasing evidence about the possibility that selected phytochemicals could lead to anesthetics and anesthesia-related drugs. Flavonoids which acts as GABAA receptor-modulators (such as apigenin, kaempferol, wogonin, and many others) may be the lead compounds for general anesthetics and sedatives. In further studies is important to clarify the adverse effect, pharmacodynamics and kinetics of these compounds, also clinical efficacy due to reduce potential toxicity and increase their activity.

Conflicts of Interest

The authors confirm that they have no conflict of interest.

References

1. Dippenaar JM. Herbal and alternative medicine: the impact on anesthesia. Southern African Journal of Anaesthesia and Analgesia 21 (2015): 8-13.
2. Frost E. Herbal medicines and interactions with anesthetic agents. Middle East Journal of Anestheiology 18 (2006): 851-878.
3. Hanrahan JM, Chebib M, Johnston GAR. Flavonoid modulation of GABAA receptors. British Journal of Pharmacology 163 (2011): 234-245.
4. Manach C, Scalbert A, Morand C, et al. Polyphenols: food sources and bioavailability. The American Journal of Clinical Nutrition 79 (2004): 727-747.
5. Tsuchiya H. Anesthetic Agents of Plant Origin: A Review of Phytochemicals with Anesthetic Activity. Molecules 22 (2017): 1-34.
6. Hanrahan JR, Chebib M, Davucheron NLM, et al. Semisynthetic preparation of amentoflavone: a negative modulator at GABAA receptors. Bioorganic and Midicinal Chemistry Letters 13 (2003): 2281-2284.
7. Adachi N, Tomonaga S, Tachibana T, et al. (–)-Epigallocatechin gallate attenuates acute stress responses through GABAergic system in the brain. European Journal of Pharmacology 531 (2003): 171-175.

8. Vignes M, Maurice T, Lanté F, et al.Anxiolytic properties of green tea polyphenol (-)-epigallocatechin gallate (EGCG). Brain Research 1110 (2006): 102-115.
9. Park KS, Han JY, Moon DC, et al. (-)-Epigallocatechin-3-O-gallate augments pentobarbital-induced sleeping behaviors through Cl- channel activation. Journal of Medicinal Food 14 (2011): 1456-1462.
10. Hui KM, Huen MS, Wang HY, et al. Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from Scutellaria baicalensis Georgi. Biochemical Pharmacology 64 (2002): 1415-1424.
11. Park HG, Yoon SY, Choi JY, et al. Anticonvulsant effect of wogonin isolated from Scutellaria baicalensis. European Journal of Pharmacology 574 (2007): 112-119.
12. Gazola AC, Costa GM, Castellanos L, et al. Involvement of GABAergic pathway in the sedative activity of apigenin, the main flavonoid from Passiflora quadrangularis pericarp. Revista Brasileira de Farmacognosia 25 (2015): 158-163.
13. Brown E, Hurd NS, McCall S, et al. Evaluation of the anxiolytic effects of chrysin, a Passiflora incarnata extract, in the laboratory rat. American association of Nurse Anesthetists Journal 75 (2007): 333-337.
14. Grundmann O, Nakajima J, Kamata K, et al. Kaempferol from the leaves of Apocynum venetum possesses anxiolytic activities in the elevated plus maze test in mice. Phytomedicine 16 (2009): 295-302.
15. Hansen RS, Paulsen I, Davies M. Determinants of amentoflavone interaction at the GABAA receptor. European Journal of Pharmacology 519 (2005): 199-207.
16. Adaramoye OA. Protective effect of kolaviron, a bioflavonoid from Garcinia kola seeds, in brain of Wistar albino rats exposed to gamma-radiation. Biological and Pharmaceutical Bulletin 33 (2010): 260-266.
17. Tchimene MK, Aanaga AO, Ugwoke CE, et al. Bio-flavonoids and garcinoic acid from Garcinia kola seeds with promising local anesthetic potentials. International Journal of Pharmacognosy and Phytochemical Research 7 (2015): 764-767.

Citation: Beata Cizmarova, Beata Hubkova, Maria Marekova, Kraus Vladimir jr, Anna Birkova. Natural Plant Compounds with Possible Interaction with Anesthetics. Anesthesia and Critical Care 1 (2019): 10-14.

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