

Bug as a Drug. *Lytta vesicatoria* L. Applications in Nineteenth Century Official Medicine

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ABSTRACT

Nowadays the limited number of animal species are used in official medicine. For example, equine urine is a source of conjugated oestrogens used in menopausal hormone therapy; porcine intestine is the only approved source of anticoagulant and antithrombotic drug—enoxaparin. Until the end of nineteenth century animal-based medicines were very popular. Raw materials included substances obtained from mammals, birds, reptiles, and insects were used. Among insects the most important were red wood ant (*Formica rufa* L.), cochineal (*Dactylopius coccus* Costa), western honeybee (*Apis mellifica* L.) and cantharides (*Lytta vesicatoria* L.). Initially this species was only gathered in Spain. Because of that, this beetle was called *Musca hispanica* (spanish fly). In subsequent years it was found in other European countries such as France, Italy, Germany, Hungary, Poland, and Great Britain. In my research I have analyzed six European state pharmacopoeias published in nineteenth century—*Pharmacopoea Regni Poloniae* (1817), *Pharmacopoea Fennica* (1819), *Pharmacopoea Bavarica* (1822), *Pharmacopoea Norvegica* (1854), *Pharmacopoea Belgica* (1854) and British Pharmacopoeia (1867). A total of 18 pharmaceutical preparations were noted. Among the analyzed sources, the most frequently reported pharmaceutical preparations were plaster of cantharides (*Emplastrum Cantharidum*) and ointment of cantharides (*Unguentum Cantharidum*)—these medications were found in all pharmacopoeias. Less common were tincture of cantharides (*Tinctura Cantharidum*), concentrated essence of cantharides (*Essentia Cantharidum Fortior*) and blistering paper (*Charta epispatica*) – they were presented in two works. Other drugs were reported individually. This study indicates the potential application of *L. vesicatoria* in contemporary medicine.

Key words: Cantharides, Ethnopharmacology, History of Pharmacy, Spanish Fly, Pharmacopoeia, Dosage forms.

INTRODUCTION

The history of humankind is strongly connected with exploitation of natural resources. Fighting against starvation and illnesses were the basis of the formation of societies. The animal raw materials were gathered and used in various branches of industry, culture, and life science. Currently limited number of animal species are used in official medicine. For example, equine urine is a source of conjugated oestrogens used in treatment of menopausal hormone therapy; porcine intestine is the only approved source of anticoagulant and antithrombotic drug—enoxaparin.^[1] But the application of animals as a source of medicinal resources in official medicine has gone. Usage of animal *materia medica* is still common in more traditional communities.^[2,3]

Until the end of nineteenth century animal-based medicines were very popular. The used raw materials include substances obtained from mammals (human skull and fat, castoreum from beavers, musk from musk deer, “unicorn horn” from narwhal), birds (faeces of peafowl), reptiles (fat and skeleton of Avicenna viper) and insects.^[4] Among insects the most important were red wood ant (*Formica rufa* L.),

cochineal (*Dactylopius coccus* Costa.), European stag beetle (*Lucanus cervus* L.), western honeybee (*Apis mellifica* L.) and cantharides (*Lytta vesicatoria* L.).^[4,5]

Lytta vesicatoria L.—source of Cantharidum

The source of described raw material is a beetle from the Meloidae family—*Lytta vesicatoria* L. This blister beetle is a slender, cylindrical insect with opalescent golden-green colour with blue gloss. It is approximately 1,5–3 cm long and 0,5–0,8 mm wide. The smell of this source is very strong with unpleasant mouse scent.^[6] The appearance of described insect is shown in Figure 1.

Initially this species was only found in Spain. For this reason, they called it *Musca Hispanica* (spanish fly). In subsequent years it was found in other European countries such as France, Italy, Germany, Hungary, Poland, Great Britain.^[7,8] The imaginal stage of this insect feed on leaves on various trees. It is being found on plants from *Oleaceae* family such as: ash (*Fraxinus* spp.), privet (*Ligustrum* spp.), lilac (*Syringa* spp.); *Caprifoliaceae*: honeysuckle (*Lonicera* spp.); *Adoxaceae*: elder (*Sambucus* spp.).^[7,9]

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Figure 1: *Lytta vesicatoria* according to *Atlas historji naturalnej* [eng. Natural History Atlas] from 1900 Public domain.^[10]

Gatherers of this raw material stretched the cloth around the tree, then shaken its branches. Fallen insects were collected into a container with water, alcohol, vinegar, or gasoline, or by exposure to the vapor of spirit, turpentine or vinegar.^[6-8] After death (in imaginal state) they were quickly dried in the sun or with artificial heat.^[6]

Powder of *L. vesicatoria* yields its active components (mainly cantharidin— tricyclic terpenoid) to alcohol, ether, fixed and volatile oils.^[8] For this mentioned reason these ingredients were used as solvents during obtaining pharmaceutical preparations. This drug was adulterated with *Cetonia aurata* L. and with euphorbium (resin obtained from various species of spurge e.g. *Euphorbia resinifera* A. Berger).^[7-8]

In this article, I wanted to find out, in which drug forms *L. vesicatoria* was used, for which diseases it was applied, and how these remedies were prepared in 19th century European pharmacy.

MATERIALS AND METHODS

Literature search

The author conducted a literature search within the archive.org database using keywords such as “Pharmacopoeia” and “Pharmacopeia”, between 1819 and 1882 (published in Europe).^[11] After reading the works, I selected the most relevant books for this article. Regarding the inclusion criteria, the works were selected depending on the inclusion based on the following topics: dosage forms of drugs based on cantharis, and their application. Exclusion criteria include the following: All other books that did not cover one of these topics as their primary endpoint. The binominal Latin names of plants were synchronized with The Plantlist database.^[12]

The author searched works mentioned in section *Sources* for pharmaceutical preparations based on grounded *L. vesicatoria*. Then the author translated and comprised these recipes, their ingredients ratios, variability, names, and applications. It was assumed, that 1 uncia (ounce) is equivalent of 1/12 of libra and 1 drachma is equivalent of 1/8 of uncia. To simplify the calculations, it was assumed that 1 fluid ounce is equal to 1 uncia.

Sources

In the research author used six European state pharmacopoeias published in nineteenth century. The first one, *Pharmacopoeia Regni Poloniae* is considered to be the first Polish national pharmacopoeia. It

was compiled by General Medical Council of the Kingdom of Poland and published in 1817 in Warsaw. This work is divided into three parts: *Materia pharmaceutica*, *Preparata et composita* and *Ex tempore parranda*.^[13]

The second source was the *Pharmacopoea Fennica*. This work was published in 1819 under the privilege of the Prince of Finland. It is divided in two parts: *Materia pharmaceutica* and *Preparata pharmaceutica*. In the preface, it is placed *Normae pharmaceuticae*—pharmaceutical standards and rules of obtaining the *materia medica*, measuring and preparation of medications.^[14]

Pharmacopoeia for the Kingdom of Bavaria or *Pharmacopoea Bavarica*, ordered by King of Bavaria was published in 1822. de Martius (probably Ernst Wilhelm Martius – German pharmacognosist and entomologist) took care of the description of medicinal raw materials (mineral, herbal and animal products). After the opening section, the medical council included *Generalia*—pharmacopoeial standard methods of measurement of density and energy (calories). The main text is divided in three volumes. First, *Tomus primus* is separated in three subsections—*materia pharmaceutica animalis* (animal sources), *materia pharmaceutica mineralis* (mineral sources), *materia pharmaceutica vegetabilis* (plant sources). Second volume, *Tomus secundus* is dedicated to synthetic and galenic pharmaceutical preparations. First subchapter—*technica pharmaceutica* lists the following formulations: acids, alcohols, tinctures, medicinal waters, medicinal powders, and other forms of the drug.^[15]

Pharmacopoea Norvegica was published in 1854 under authority of king Oscar I of Sweden. It was first Norwegian national pharmacopoeia. This book is not divided in parts like the other ones pharmacopoeias. The main text is composed of descriptions of pure substances, raw materials and pharmaceutical preparations arranged in alphabetical order.^[16]

New Belgian Pharmacopoeia or *Pharmacopoea Belgica Nova* is an 1854 successor of previous *Pharmacopoea Belgica*. This volume starts from pharmacopoeial standard methods of measurement. The main text is divided into sections dedicated to *materia medica*, pharmaceutical preparations, special drugs, and antidotes.^[17]

The last pharmacopoeia used in research is British Pharmacopoeia from 1867. It was published under the direction of president of The General Council of Medical Education and Registration of the United Kingdom—dr. George Burrows. It was the first pharmacopoeia which replaced the previous local indices of medicines of British Isles. The main text is composed of descriptions of pure substances, raw materials and pharmaceutical preparations arranged in alphabetical order (like in *Pharmacopoea Norvegica*). The interesting part is tables, which describe the weight and measures standards, pharmaceutical symbols and books containing plates of officinal plants.^[18]

RESULTS

Original Medicinal Uses

Carl Linnaeus in his well-known work about crude drugs—*Materia medica per regna tria naturae* [Medicinal sources from three kingdoms of nature] describes all species of animals and plants which was used in pharmacy and medicine in his contemporary times. In the chapter devoted to insects he described the cantharid under the name *Meloë vesicatorius*.^[4] This description has been placed above with the author’s translation.

Original Latin text

VIS: inter. diuretica! aphrodisiaca, exter. corrosiva, exulcerans, excitans, revellans

USUS: intern. Ischuria, Hydrophobia, Hydrops, Gonorrhoea maligna. Exter. Febr- exanth maligna, Pleuritis, Morbi soporosi, Delirium, Ophthalmia, Paralysis, Asthma, Ulcera cacoëthica

Translation

Potency: internal [usage] diuretic! aphrodisiac, external [usage] irritating, fomentative, rousing, revulsive

Usage: internal [usage] ischuria, rabies, oedema, lues maligna. External [usage] maligna hyperthermia, pleurisy, coma, delirium, ophthalmitis, paralysis, asthma, necrotizing fasciitis

Pharmaceutical preparations based on *L. vesicatoria*

Pharmacopoeia Regni Poloniae (1817)^[13]

In *materia medica* part of *Pharmacopoeia Regni Poloniae* (Pharmacopoeia of Kingdom of Poland) the description of Cantharides has been placed alongside their appearance, foraging place, and method of obtaining. What is remarkable, the polish synonym of this source *Muchy Hiszpańskie* was also provided. The first analyzed formula is *Emplastrum Cantharidum Ordinarium* (basic plaster of cantharides; page 106). It contains 1 libra of beeswax, 3 unciæ of turpentine and purified pork lard and half unciæ of ground cantharides (Figure 2). The first three ingredients were melted, then the powder of *L. vesicatoria* was added, mixed and the plaster were formulated. The ratio of used ingredients is 24:6:6:1 (beeswax: turpentine: lard: cantharides).^[13]

Second plaster mentioned in this volume is *Emplastrum Cantharidum Perpetuum* (constant plaster of cantharides; page 107). It was composed of 2 unciæ of grounded cantharides, 1 unciæ of euphorbium (resin obtained from *E. resinifera*) and one libra of turpentine and pine resin (obtained from *Pinus sylvestris* L.). The process of formulation was analogical to the previous one (melting and mixing the resins, then adding the cantharides. The ratio of used ingredients is 1:12:12:2 (euphorbium: turpentine: pine resin: cantharides).

Tinctura Cantharidum (tincture of cantharides; page 167) according to this pharmacopoeia consist of half unciæ of cantharides and 1 libra of spirit. Raw material was macerated in alcohol in cold place for 3 days and filtered. The ratio of used ingredients is 24:1 (alcohol: cantharides).

Unguentum Cantharidum (ointment of cantharides; page 175) was compounded by mixing 2 unciæ of crashed cantharides with 8 unciæ of poppyseed oil (obtained from *Papaver somniferum* L.) and heating in water bath. After 2 hr the mixture was strained and half libra of this compound was added to 4 unciæ of beeswax. The ratio of used ingredients in final product is 4:4,8:1,2 (beeswax: oil: cantharides).

Pharmacopoea Fennica (1819)^[14]

In another European state pharmacopoeia—*Pharmacopoea Fennica* (Finnish Pharmacopoeia) first recipe based on blister beetle is *Emplastrum*

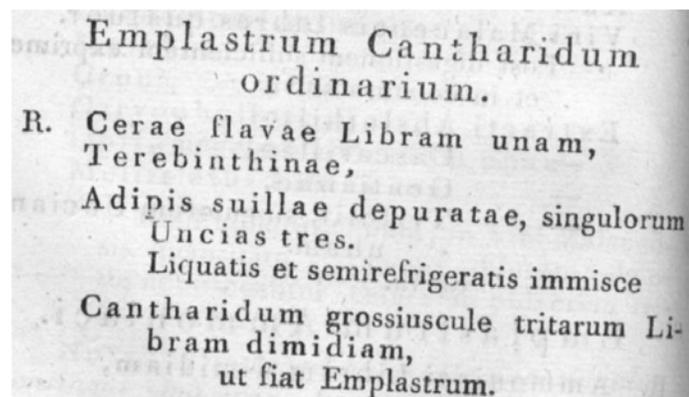


Figure 2: Recipe for basic plaster of cantharides according to *Pharmacopoeia Regni Poloniae* (1817), Public domain.^[13]

Cantharidum (plaster of cantharides; page 48). It consisted of 10 unciæ of beeswax, 3 unciæ of turpentine and olive oil (obtained from *Olea europaea* L.) and 6 unciæ of cantharides. Oil, wax, and turpentine was melted, then the grinded cantharides were added. This mixture was heated on the fire for hour, then strained and cooled. The ratio of used ingredients is 10:3:3:6 (beeswax: turpentine: oil: cantharides).^[14]

Tinctura cantharidum (tincture of cantharides; page 85) was prepared by maceration of 0,5 unciæ of cantharides in 1 libra of spirit in cold place for 8 days. Then the tincture was strained through the filtration paper. The ratio of used ingredients is 24:1 (alcohol: cantharides).

Unguentum Cantharidum (ointment of cantharides; page 91) was compounded by mixing 1 libra of cantharides with 4 librae of *Unguenti terebinthinae resinosi* (3 unciæ of rosin, lanolin, turpentine, and beeswax heated and mixed with libra of olive oil). The ratio of used ingredients in final product is 1:1:4:1:1:2 (beeswax: turpentine: oil: lanolin: rosin: cantharides).

Second ointment mentioned in this work is *Unguentum Cantharidum Colatum* (filtered plaster of cantharides; page 92). It was prepared by mixing 1 libra of above medicine – ointment of cantharides, filtered through linen cloth with 2 drachmae of copper(II) sulfate with 1 libra of olive oil (Figure 3). The ratio of used ingredients is 12:12:0,25 (cantharides ointment: olive: copper(II) sulfate).

Pharmacopoea Bavarica (1822)^[15]

In one of German state Pharmacopoeia—Bavarian Pharmacopoeia (*Pharmacopoea Bavarica*) there is no description of *L. vesicatoria* as a crude drug. Nevertheless, there is several recipes based on described insect. The first of these is *Alcohol Cantharidum* (tincture of cantharides; page 161). This drug was formulated by simple maceration one part of cantharides in 6 parts of spirit for 3 days. This brown tincture turned green when water was added (Figure 4).

Emplastrum Cantharidum Cereum (plaster of cantharides with wax; page 185) was manufactured by melting 4 parts of beeswax with 1 part of olive oil. Then 1 part of turpentine and 2 parts of ground cantharides

UNGUENTUM CANTHARIDUM COLATUM.

UNGUENTUM AD FONTICULOS BERGII.

Unguentum cantharidum adhuc calidum coletur per linteam. Libræ ejus uni addantur

Aeruginis pulveratæ Drachmæ tres, cum æquali quantitate

Olivarum olei

subtilissime contritæ.

Figure 3: Recipe for filtered cantharis plaster according to *Pharmacopoea Fennica* (1819), Public domain.^[14]

ALCOHOL CANTHARIDUM. Tinctura Cantharidum O.

Para ex parte una Cantharidum, in sex partibus Alcoholis diluti per tres dies macerandis.

Sit brunneum; saporis caustici; addita Aqua colore flavo-virente oppalescens.

Figure 4: Recipe for tincture of cantharides according to *Pharmacopoea Bavarica* (1822), Public domain.^[15]

were added to this mixture. This formula ends with a warning of the dangerous effects of this medicine (toxicity).

The last formula incorporated in this pharmacopoeia is *Unguentum Cantharidum Cereum* (ointment of cantharides with wax; page 268). It was prepared by digestion 1 part of cantharides with 2 parts of spirit for 24 hr. Then 4 parts of almond oil (*Prunus dulcis* (Mill.) D.A. Webb) were added, mixed and heated until all the alcohol has been vaporized. In last step this blend was heated with 1,5 parts of beeswax.

Pharmacopoea Norvegica (1854)^[16]

In *Pharmacopoea Norvegica* (Norwegian Pharmacopoeia) first mentioned prescription was for *Emplastrum Cantharidum Colatum* (filtered plaster of cantharides; page 40). This medicine was prepared by mixing (in porcelain or copper container) 8 parts of pulverized *L. vesicatoria* and rosin, 5 parts of beeswax and 2 parts of tallow (obtained from *Bos taurus* L.). Then the vessel was heated in water bath till the fusion of all compounds. In next step 1 part of *Picea abies* (L.) H. Karst or *P. sylvestris* turpentine was added. In the last step the mixture was cooled and put on special sheet.

Emplastrum Cantharidum Ordinarium (ordinary plaster of cantharides; page 40) was formulated by mixing and heating 10 parts of beeswax, 3 parts of turpentine and oil, and 6 parts of powder of cantharides.

Emplastrum Cantharidum Perpetuum (constant plaster of cantharides; page 41) was prepared by incorporation the following components: 12 parts of melted turpentine and mastic (obtained from *Pistacia lentiscus* L.), 3 parts of ground cantharides and 2 parts of pulverized euphorbium. In the last step the mixture was cooled and put on special sheet (Figure 6).

This pharmacopoeia contains two recipes for tinctures: *Essentia Cantharidum* (essence of cantharides; page 50) and *Essentia Cantharidum Fortior* (concentrated essence of cantharides; page 50). The only difference between these two formulations were ingredients ratio: 1:30 in first and 1:5 in second formula. These essences were produced by digestion the pulverized *L. vesicatoria* under reflux condenser.

Oleum Cantharidum Infusum (infused oil of cantharides; page 103) was prepared by heating the vessel with 1 part of pulverized Spanish fly with 4 parts of oil in steam bath for 6 hr and filtration of medicine.

Recipe for *Unguentum Cantharidum* (ointment of cantharides; page 174). was almost the same as *Emplastrum Cantharidum Colatum*. The only difference was ratio—1 part of colophony, tallow and beeswax was mixed with 2 parts of ground cantharides, 4 parts of oil and heated in 90–100 Celsius degrees. In the next step 1 part of turpentine was added (Figure 5).

Pharmacopoea Belgica nova (1854)^[17]

The New Belgian Pharmacopoeia (*Pharmacopoea Belgica nova*) contains the highest number of recipes among the analyzed pharmacopoeias (de Hemptinne 1854). The method of preparation of plasters is comparable to those mentioned earlier. *Emplastrum Cantharidum* (plaster of cantharides; page 161) was prepared by mixing 480 parts of beeswax, 420 parts of Venetian turpentine (obtained from *Larix decidua* Mill.), and olive oil with 280 parts of pulverized *L. vesicatoria*. *Emplastrum Cantharidum Anglicum* (English plaster of cantharides; page 161) was formulated by mixing 203 parts of beeswax and lanolin, 94 parts of rosin, 169 parts of pork lard with 332 parts of pulverized cantharides. *Emplastrum Cantharidum Camphoratum* (camphor plaster of cantharides; page 162) was compounded by mixing 96 parts of above plaster of cantharides with 4 parts camphor with small amount of olive oil. The last plaster—*Emplastrum Cantharidum Perpetuum* (constant plaster of cantharides; page 162) was prepared by mixing 387 parts of



Figure 5: Apothecary ointment of cantharides jar. From collection of Sverresborg Trøndelag Folkemuseum (Norway). CC BY-NC-SA 4.0 license.

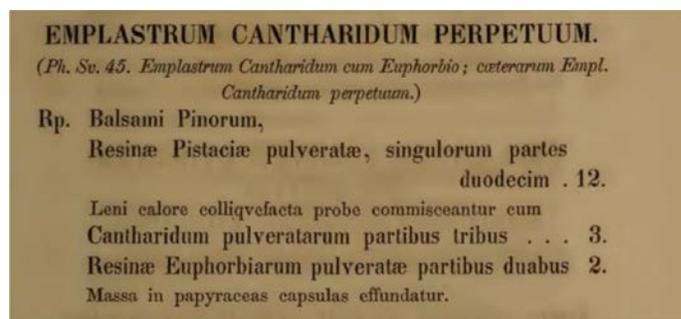


Figure 6: Recipe for constant plaster of cantharides according to Pharmacopoea Norvegica (1854), Public domain.^[16]

mastic, 387 parts of Venetian turpentine, 33 parts of pork lard with 64 parts of pulverized euphorbium and 429 parts of cantharides.

Oleum cantharidatum (oil of cantharides; page 202) was prepared in a unique way 100 parts of pulverized cantharides were boiled with 500 parts of water for 6 hr. In the next step this decoction was strained and reduced into 300 parts in bain-marie. In last step 1000 parts of olive oil was poured and gently heated for 15 min; then the mixture was cooled, and the oil phase was separated from water.

Tinctura Cantharidum Aetherea (ethereal tincture of cantharides; page 264) was done by simple percolation of 200 parts of ground

L. vesicatoria with 400 parts of ether. After 20 hr tincture was collected and once again 400 parts of solvent were added. After 6 hr of second percolation following part of tincture was collected. The remaining raw material was pressed out; squeezed fluid was added to previous part of tincture and the ether was poured up to 1000 parts of tincture.

In the described pharmacopoeia were found four recipes for ointment. First, *Unguentum Cantharidum Album* / *Unguentum Perpetuum* (white ointment of cantharides /constant ointment of cantharides; page 274) was prepared by boiling 100 parts of ground cantharides with 1000 parts of water for 6 hr. Then decoction was strained and reduced to 6 parts. In next step 857 parts of pork lard and 143 parts of beeswax were added and this mixture was heated for 15 min. In last step this medicine was cooled, and water part was removed.

Unguentum Cantharidum Nigrum (black ointment of cantharides; page 274) and *Unguentum Cantharidum Viride* (green ointment of cantharides; page 275) were compounded medicines. In first case it was mixture of 150 parts of cantharides and 850 parts of simple ointment (850 parts of port lard, 150 parts of beeswax). In second case it was mixture of 30 parts of cantharides, 319 parts of olive oil, 175 parts of beeswax and 476 parts of poplar ointment (200 parts of *Populus* spp. buds, 125 parts of *Hyoscyamus niger* L. and *Atropa belladonna* L. leaves, 500 parts of water and 1000 parts of pork lard).

Charta epispatica (blistering paper; page 319) was prepared by immersion of paper in melted mixture of 78–90 parts of crushed *L. vesicatoria*, 433 parts of beeswax, 217 parts of spermaceti (obtained from *Physeter macrocephalus* L.), 217 parts of oleoresin Elemi (obtained from *Canarium luzonicum* (Blume) A.Gray), and 153 parts of Venetian turpentine.

Collodium cantharidatum (collodion of cantharides; page 320) was formulated in two phases. In first one 500 parts of ground cantharides were percolated in mixture of 500 parts of ether and 90 parts of ethyl acetate. In second phase 100 parts of this extract were mixed with 2 parts of cellulose nitrate (Figure 8).

British Pharmacopoeia (1867)^[18]

Acetum cantharidis (vinegar of cantharides; page 2) was prepared by mixing 13 fluid ounces of acetic acid with 2 ounces of anhydrous acetic acid. Then in this blend 2 ounces of cantharides in powder was poured and digested for 2 hr in 93 Celsius degree. In next step this mixture was put into percolator, and when the liquid ceased to pass, 5 fluid ounces of acetic acid over the residuum in the apparatus were poured. As soon as the percolation were complete, the liquids were mixed with enough acetic acid to get 20 fluid ounces. The ratio of used ingredients is 20:2 (vinegar:cantharides).

Emplastrum cantharidis (cantharis plaster; page 105) was prepared by liquidation of 7,5 unciæ of beeswax and suet (obtained from *B. taurus*) and 6 unciæ of lard on water bath. Then 3 unciæ of resin and 12 unciæ

UNGUENTUM CONTRA CALVITIEM (DUPUYTREN).

R. Extracti Cantharidum alcoholici. . part.	2
Olei Amygdalarum »	58
Balsami nervini. »	470
Medullæ bovinæ »	470
	<hr/>
	1000

Figure 7: Recipe for Unguentum Contra Calvitem (ointment against baldness; page 341). Public domain.^[17]

COLLODIUM CANTHARIDATUM.

R. Cantharidum pulveratarum part.	500
Ætheris sulphurici »	500
— acetici »	90

Methodo lixivatoria exhausta et residuum ope preli exprime; tunc sume

Hujus soluti ætherici. part.	100
Pyroxyli »	2

Pyroxylum solutum servetur vase probe clauso.

Nota. Liquidum hoc, ope penicilli cuti applicatum, vesicationem producit.

Figure 8: Recipe for collodion of cantharides according to Pharmacopoeia Belgica Nova. Public domain.^[17]

of cantharides were added. The ratio of used ingredients is 7,5:7,5:6:3:12 (beeswax:suet:lard:resin:cantharides).

Tinctura Cantharidis (tincture of cantharides; page 323) was prepared by simple maceration of 0,25 unciæ of ground *L. vesicatoria* in 20 liquid ounces of spirit for 7 days. The ratio of used ingredients is 80:1 (spirit:cantharides).

Unguentum Cantharidis (ointment of cantharides; page 353) was compounded by infusion of 1 unciæ of cantharides in 6 fluid ounces of olive oil for 12 hr. Then this medicinal oil was put in baine-marine for 15 min and strained. In last step 1 unciæ of beeswax was added. The ratio of used ingredients is 6:1:1 (oil:wax:cantharides)

Unguentum contra calvitem (ointment against baldness) was prepared by mixing the nervine ointment (470 parts) with almond oil (*Prunus dulcis* (Mill.) D.A.Webb) (58 parts), extract of cantharides (2 parts) and bovine bone marrow (470 parts) (Figure 7).

DISCUSSION AND CONCLUSION

The raw material described above was used externally mainly as blistering agent and local irritant; also, in chronic gonorrhoea, paralysis, lepra, ulcers therapy. Spanish fly was used internally as a diuretic stimulant and aphrodisiac. In large doses it is a very dangerous poison causing severe inflammation and irritation of internal organs. In acute poisoning suppression of urine, excessive priapism, headache, delirium, convulsions, coma, and death were observed. Lethal dose is 1,6 g of *L. vesicatoria*, what is equivalent of 10–50 mg of pure cantharidin.^[8]

The pharmacists and doctors in nineteenth century believed, that the best pharmaceutical form (used internally) based on cantharides is tincture. The plasters (*Emplastra*) based on Cantharidum were held on skin for 2–3 hr.^[6] If Carried longer (4–5 h) large blisters were produced. After 24 hr yellow liquid is produced, and hard healing wounds are formed. They could heal even for six months.^[7]

According to some authors the aphrodisiac effect occurs only in subtoxic dose.^[6] Moreover, they believed that this action is possible when cantharidin is absorbed into the bloodstream.^[6] It is worth to notice, that this substance may irritate the urethra when excreted in urine, resulting in the congestion of the reproductive organs.^[6,8]

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Table 1: The comparison of drugs described in various pharmacopoeias.^[13–18]

Pharmaceutical preparation	Ph. Reg. Pol. 1817	Ph. Fenn. 1819	Ph. Bav. 1822	Ph. Norv. 1854	Ph. Belg. 1854	Ph. Br. 1867
<i>Acetum cantharidis</i>	-	-	-	-	-	+
<i>Charta epispatica</i>	-	-	-	-	+	+
<i>Collodion cantharidatum</i>	-	-	-	-	+	-
<i>Emplastrum calefaciens</i>	-	-	-	-	-	+
<i>Emplastrum Cantharidum Camphoratum</i>	-	-	-	-	+	-
<i>Emplastrum Catharidum Colatum</i>	-	-	-	+	-	-
<i>Emplastrum Cantharidum (Ordinarium/Cereum)</i>	+	+	+	+	+	+
<i>Emplastrum Cantharidum Perpetuum</i>	+	-	-	+	+	-
<i>Essentia/Tinctura/Alcohol Cantharidum</i>	+	+	+	+	-	+
<i>Essentia Cantharidum Fortior</i>	-	-	+	+	-	-
<i>Oleum Cantharidum Infusum</i>	-	-	-	+	+	-
<i>Tinctura Cantharidum Aetherea</i>	-	-	-	-	+	-
<i>Unguentum Cantharidum (Cereum)</i>	+	+	+	+	-	+
<i>Unguentum Cantharidum Album</i>	-	-	-	-	+	-
<i>Unguentum Cantharidum Colatum</i>	-	+	-	-	-	-
<i>Unguentum Cantharidum Nigrum</i>	-	-	-	-	+	-
<i>Unguentum Cantharidum Viride</i>	-	-	-	-	+	-
<i>Unguentum Contra Calvittem</i>	-	-	-	-	+	-

Legend: Ph. Reg. Pol.—Pharmacopoeia Regni Poloniae, Ph. Fenn. —Pharmacopoea Fennica, Ph. Bav—Pharmacopoea Bavarica, Ph. Norv—Pharmacopoea Norvegica, Ph. Br.—British Pharmacopoeia.

cantharidin is absorbed into the bloodstream.^[6] It is worth to notice, that this substance may irritate the urethra when excreted in urine, resulting in the congestion of the reproductive organs.^[6,8]

Among the analyzed sources, the most frequently reported pharmaceutical preparations are plaster of cantharides (*Emplastrum Cantharidum*) and ointment of cantharides (*Unguentum Cantharidum*)—these medications were found in all pharmacopoeias. Less common were tincture of cantharides (*Tinctura Cantharidum*), concentrated essence of cantharides (*Essentia Cantharidum Fortior*) and blistering paper (*Charta epispatica*)—they were present in two works. Other drugs were reported individually.

The described formulae for the tincture of cantharides differ from the recipe mentioned in P. Hernquist manuscript *Zoopharmacologia* from the first part of nineteenth century.^[19] According to L. E. Appelgren (2010) this preparation was formulated by maceration of 3 unciae of cantharides with 0,5 uncia of camphor and 1,5 drachms of nitric acid in 1 measure [sic] of spirit. After the appropriate number of days, it was filtrated. In described formulae alcoholic tincture was prepared by simple maceration and filtration of crude drug. P. Hernquist also supposedly describe irritating, proinflammatory and diuretic properties of *Lytta vesicatoria* and its products.^[19] This description of pharmacological properties is identical to these mentioned by Carl Linnaeus (1772) and editors of state pharmacopoeias.

The biggest noted concentrations of cantharides were 34%—*Emplastrum Catharidum Colatum* (Norwegian Pharmacopoeia). Slightly lower (33%) in the case of *Emplastrum Cantharidum Perpetuum* (New Belgian Pharmacopoeia) and *Emplastrum Cantharidis* (British Pharmacopoeia). The comparison of drugs mentioned in described sources is shown in Table 1.

Currently the cantharidin in US, in the form of collodion, is used in the treatment of warts and molluscum. The most common concentration of this terpenoid, used in these medications, is 0,7%.^[20] It was also proven

that this substance act as a vasoconstrictor in human cardiac tissue (Puerto Galvis *et al.* 2013). Other compounds, based on cantharidin (norcantharidin, cantharidimide, norcantharimide), because of their inhibitory activity of phosphoprotein phosphatases could be efficient in treatment of cancer.^[21] This study indicates the potential applications of *L. vesicatoria* in contemporary medicine. Also, it may inspire further clinical trials and research.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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