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The real Theriac – panacea, poisonous drug or quackery?

Danuta Raj [a,*], Katarzyna Pękacka-Falkowska [b], Maciej Włodarczyk [a], Jakub Węglorz [c]

[a] Department of Pharmacognosy and Herbal Medicines, Wroclaw Medical University, Borowska 211a, 50-556, Wrocław, Poland
[b] Department of History and Philosophy of Medical Sciences, Poznań University of Medical Sciences, Przybyszewskiego 37, 60-356, Poznan, Poland
[c] Historical Institute, University of Wrocław, Szewska 49, 50-139, Wrocław, Poland

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ABSTRACT

Ethnopharmacological relevance: Theriac is considered the most popular cure-all multi-ingredient medicine and has been used for more than two millennia. It has also been used as one of the most important anti-epidemic drugs up to the 19th c., treated as an emergency medicine in case of e.g. bubonic plague. Aim of the study: Until now, no reliable information regarding the pharmacological effect of the treacle was available, including its possible toxic or narcotic properties. In order to change the state of knowledge in this matter we have selected the Theriac recipe that had been actually used for producing the treacle in 1630, which was confirmed by the official municipal documents of the time.

Methods: The recipe was written in Latin, with the use of pre-Linnean nomenclature and then apothecary common names, which required translation into the modern scientific language in order to get reliable pharmacological conclusions. The information from historical sources has been compiled with the pharmacological data concerning the most potent compounds, which for the first time made it possible to calculate the amounts of active compounds in the doses taken by then patients.

Results: Only two species included in Theriac can be harmful in humans: poppy and sea squill, but in both cases the calculated quantity of morphine and cardiac glycosides, respectively, were below toxic level. There are no indications, both from the historical and pharmacological point of view, for Theriac being toxic or narcotic in patients, when used as prescribed.

Conclusions: As for now, the most probable is that the treacle owed its postulated efficacy in the main indications to the placebo effect. Still, the results should be further confirmed by reconstructing the actual Theriac and subjecting it to modern tests and analyses.

1. Introduction

Theriac is considered to be a combined preparation with the longest history of use. The origins of its name and the opinions on its roots were widely discussed at the time of its popularity (Grévin, 1568). According to most likely information the first known formula, which became the basis of the drug, was developed in the 3rd c. BC by Mithridates VI, King of Pontus, as an antidote against poisoning. Initially, it consisted of 36–54 ingredients (Karamanou and Androutsos, 2019). Four centuries later, Andromachus, Nero's personal physician, altered the recipe by adding viper flesh and increasing the number of compounds. To distinguish between the two preparations, the older formulation was named Mithridatium, whereas the latter became known as Theriac of Andromachus. In the Middle Ages, Theriac evolved from an antidote into a panacea that entered official dispensaries and pharmacopoeias. In early modern Europe, the most famous and expensive type of the treacle was Theriac of Venice (Tidicaeus, 1607), yet the drug was also manufactured in other European cities (usually with a slightly modified formula) by selected professionals granted with an official permission (Griffin, 2004).

Although the treacle's reputation was not broken until the 19th century, it was questioned even in Ancient Rome, with Pliny the Elder being one of the most notable critics accusing the preparation of an excess of form over content (Catellani and Console, 2007). Still, it remained very popular throughout the ages, considered by some early modern physicians as the best medicine invented by man (Bonnemain, 2010). However, in the late 18th c. the popularity of Theriac started to decline and during the following century it was virtually excluded from the official therapeutic armamentarium. Nevertheless, even nowadays preparations under the name Theriac are commercially available,

* Corresponding author.
E-mail address: danuta.raj@umed.wroc.pl (D. Raj).

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although they share little resemblance to the original recipe.

In the present scientific discussion, Theriac – despite being widely recognised as the panacea used for almost two millennia – is not perceived as a set of specific ingredients, but rather as a stereotypical "mixture". Moreover, even the papers investigating the use of the drug are often generally stating that Theriac was composed of few ingredients mentioned by name, (viper flesh, opium, wine, honey and cinnamon are the most frequently listed (Bierman, 1994; Fabbri, 2007; Karaberopoulos et al., 2012; Karamanou and Androutsos, 2019)), and a group of sixty or more unnamed medical "simples" (single, mostly plant-derived compounds). Additionally, after the COVID-19 outbreak, both scholars and the general public started to pay more and more attention to historical and legendary anti-epidemic remedies such as Venetian treacle or four thieves vinegar. Yet, they did not determine the real ingredients of such potions, and, thus, unconsciously perpetuated numerous stereotypes on historical drug (Withington, 2020). Consequently, the above-mentioned study limitation negatively affects the conclusions that could be drawn on the treacle's efficacy. One of the widely accepted facts about Theriac is that it contained toxic compounds, among which opium is considered the most important and the main contributor to the drug's popularity (Ahnfelt and Fors, 2016; Karamanou and Androutsos, 2019).The information on the postulated toxicity and narcotic properties, however, is not based on an analysis of recipes actually used, especially with regard to quantitative data. This is largely due to the fact that the recipes were complex and difficult to define, as they include pre-Linnean nomenclature and customary synonymic names that can be misleading for contemporary researchers.

In Europe, until the Enlightenment, Theriac was one of the most important drugs used by people at risk of infectious diseases and epidemics (Griffin, 2004). Just like during the COVID-19 pandemic outbreak, people back-then were looking for an effective medicine that would protect them from the disease or help them to survive the infection. Consequently, Theriac was being prepared during epidemics, especially the plague (Black Death), in large quantities as a form of emergency medicine (Griffin, 2004). Yet, it was also manufactured when an epidemic threat was ceased serving as a panacea. In the latter case, the treacle preparations were important public events that could have been reported in official documents along with the actual recipes. An example of such a preserved Theriac recipe is the print published in Thorn (present-day Toruń, Poland) in 1630 by Paul Guldenius, the city apothecary. The hereby conducted scientific analysis of the historical recipe would give the first reliable information on the possible pharmacological effect of Theriac.

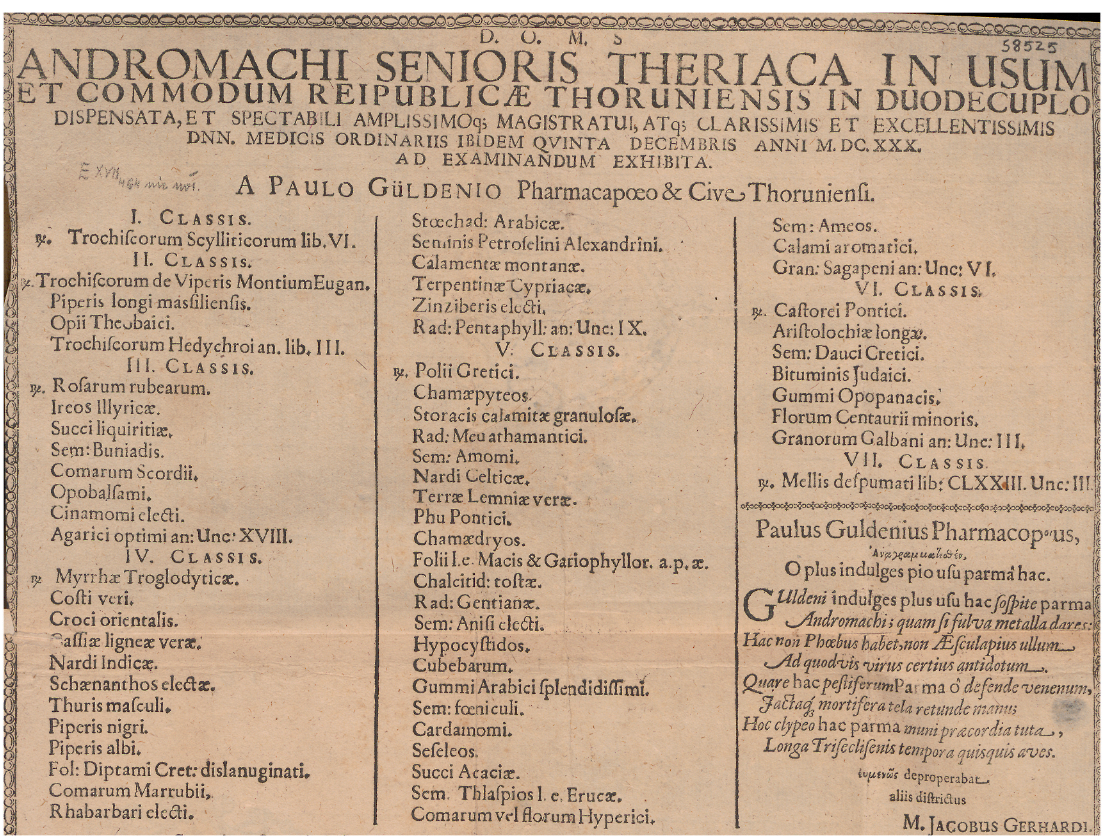
2. Methods

2.1. Theriac recipe

The Theriac recipe elaborated by Paul Guldenius was printed in Thorn in 1630 as a one-sided single-sheet flyer in the Franciscus Schnellboltz print house. The language of the recipe is Latin. One of the two surviving copies, held by the Early Books and Printed Materials Department of the Gdansk Library of the Polish Academy of Sciences, was used (Fig. 1).

For the combined preparations that are the part of Guldenius Theriac recipe but are not detailed in the print, namely Trochisci scyllitici, Trochisci de Viperis, and Trochisci Hedychroi, the recipes were taken from Dispensatorium by Valerius Cordus (Cordus Dispensatory) (Cordo, 1562).

For the quantitative calculations the conversion of the early modern period apothecary units into grams was carried according to the data presented in Table 1.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ANDROMACHI SENIORIS THERIACA IN USUM ET COMMODUM REIPUBLICÆ THORUNIENSIS IN DUODECUPLO DISPENSATA, ET SPECTABILI AMPLISSIMOq; MAGISTRATUI, ATq; CLARISSIMIS ET EXCELLENTISSIMIS DNN. MEDICIS ORDINARIIS IBIDEM QVINTA DECEMBRIS ANNI M. DC. XXX. AD EXAMINANDUM EXHIBITA.
A PAULO GÜLDENIO Pharmacapœo & Cive Thorunienſi.

I. CLASSIS.
℞. Trochiſcorum Scylliticorum lib. VI.
II. CLASSIS.
℞. Trochiſcorum de Viperis Montium Eugan.
Piperis longi masſilienſis.
Opii Thebaici.
Trochiſcorum Hedychroi an. lib. III.
III. CLASSIS.
℞. Roſarum rubearum.
Ireos Illyricæ.
Succi liquiritiæ.
Sem: Buniadis.
Comarum Scordii.
Opobalſami.
Cinamomi electi.
Agarici optimi an: Unc: XVIII.
IV. CLASSIS.
℞. Myrrhæ Troglodyticæ.
Coſti veri.
Croci orientalis.
Caſſiæ ligneæ veræ.
Nardi Indicæ.
Schænanthos electæ.
Thuris maſculi.
Piperis nigri.
Piperis albi.
Fol: Diptami Cret: dislanuginati.
Comarum Marrubii.
Rhabarbari electi.
Stœchad: Arabicæ.
Seminis Petroſelini Alexandrini.
Calamentæ montanæ.
Terpentinæ Cypriacæ.
Zinziberis electi.
Rad: Pentaphyll: an: Unc: IX.
V. CLASSIS.
℞. Polii Cretici.
Chamæpytcos.
Storacis calamitæ granuloſæ.
Rad: Meu athamantici.
Sem: Amomi.
Nardi Celticæ.
Terræ Lemniæ veræ.
Phu Pontici.
Chamædryos.
Folii I. e. Macis & Gariophyllor. a. p. æ.
Chalcitid: toſtæ.
Rad: Gentianæ.
Sem: Aniſi electi.
Hypocyſtidos.
Cubebarum.
Gummi Arabici ſplendidiſſimi.
Sem: fœniculi.
Cardamomi.
Seſeleos.
Succi Acaciæ.
Sem. Thlaſpios I. e. Erucæ.
Comarum vel florum Hyperici.
Sem: Ameos.
Calami aromatici.
Gran: Sagapeni an: Unc: VI.
VI. CLASSIS.
℞. Caſtorei Pontici.
Ariſtolochiæ longæ.
Sem: Dauci Cretici.
Bituminis Judaici.
Gummi Opopanacis.
Florum Centaurii minoris.
Granorum Galbani an: Unc: III.
VII. CLASSIS.
℞. Mellis deſpumati lib: CLXXIII. Unc: III.

Paulus Guldenius Pharmacopœus,
O plus indulges pio uſu parmâ hac.
Guldeni indulges plus uſu hac ſoſpite parma
Andromachi; quam ſi fulva metalla dares:
Hac non Phœbus habet, non Æſculapius ullum
Ad quodvis virus certius antidotum.
Quare hac peſtiferum Parma ô defende venenum,
Jactaq; mortifera tela retunde manus.
Hoc clypeo hac parma muni præcordia tuta,
Longa Triſecliſenis tempora quisquis aves.
deproperabat
aliis diſtrictus
M. JACOBUS GERHARDI.

Fig. 1. The printed Paul Guldenius Theriac recipe (Gdansk Library of the Polish Academy of Sciences).

Table 1
The Nuremberg apothecaries' weight system (Massey, 2017; Proń, 1967): a standard for most of the north-east of Europe from the mid-16th to the late 18th centuries.

lb pound (*libra Norica*)	℥ ounce (*uncia*)	℥ß lot* (*loth*)	ʒ drachm/dram (*dragma*)	℈ scruple (*scropulus*)	G grain (*granum*)
12 ounces					
24 lots	2 lots				
96 drams	8 drams	4 drams			
288 scruples	24 scruples	24 scruples	3 scruples		
5760 grains	480 grains	240 grains	60 grains	20 grains	
≈ 360 g	≈ 30 g	≈ 15 g	≈ 3.73 g	≈ 1.25 g	≈ 0.062 g

* off-system measurement unit used by Central European apothecaries (e.g. in the Polish-Lithuanian Commonwealth, German-speaking territories) in the Early Modern period.

Table 2
The translation of the Guldenius Theriac recipe.

Original name	Identification	Calculated quantity [g]	Origin[a]
1 Class			
Trochisci Scyllitici	combined preparation	2163	see Table 3
2 Class			
Trochisci de Viperis Montium Eugan	combined preparation	1082	see Table 3
Piper longum massiliense	*Piper longum* L., fruit	1082	Asia
Opium Theobaicum	*Papaver somniferum* L., latex	1082	Asia
Trochisci Hedychroi	combined preparation	1082	see Table 3
3 Class			
Rosa rubea	*Rosa* spp., red petals	541	Europe
Iris Illyrica	*Iris* × *germanica* L., rhizome	541	Europe
Succus liquiritiae	*Glycyrrhiza glabra* L., dried aequous extract (or sap) from roots	541	Europe
Semen Buniadis	*Brassica napus* L., seed	541	Europe
Coma Scordii	*Teucrium scordium* L., leaves and flowers	541	Europe
Opobalsamum	*Commiphora gileadensis* (L.) C.Chr., oleoresin	541	Africa
Cinnamomum electum	*Cinnamomum verum* J.Presl, bark	541	Asia
Agaricus optimus	*Fomitopsis officinalis* (Vill.) Bondartsev & Singer, fruitbody	541	Europe
4 Class			
Myrrha Troglodytica	*Commiphora myrrha* (Nees) Engl., oleoresin	240	Africa
Costus verus	*Saussurea costus* (Falc.) Lipsch., root	240	Asia
Crocus orientalis	*Crocus sativus* L., stigma	240	Europe
Cassia lignea vera	*Cinnamomum cassia* (L.) J.Presl, bark	240	Asia
Nardus Indica	*Nardostachys jatamansi* (D.Don) DC., root	240	Asia
Schoenanthus electus	*Cymbopogon schoenanthus* (L.) Spreng., herb	240	Africa
Thus masculum	*Boswellia* spp., oleoresin	240	Africa
Piper nigrum	*Piper nigrum* L., unripe fermented fruit	240	Asia
Piper album	*Piper nigrum* L., ripe decorticated fruit	240	Asia
Folium Diptami Cretici dislanuginatum	*Cistus creticus* L., hairless leaf	240	Europe
Coma Marrubii	*Marrubium vulgare* L., shoot top	240	Europe
Rhabarbarum electum	*Rheum. palmatum* L., root	240	Asia
Stoechas Arabica	*Lavandula stoechas* L., flower	240	Europe
Semen Petroselini Alexandrini	*Smyrnium olusatrum* L., fruit	240	Europe
Calamenta montana	*Clinopodium nepeta* (L.) Kuntze, herb	240	Europe
Terpentina Cypriaca	*Pinus* spp., oleoresin	240	Europe
Zinziber electum	*Zingiber officinale* Roscoe, rhizome	240	Asia
Radix Pentaphylli	*Potentilla reptans* L., rhizome	240	Europe
5 Class			
Polium Creticum	*Teucrium montanum* L., herb	180	Europe
Chamaepytys	*Ajuga chamaepitys* (L.) Schreb., herb	180	Europe
Storax calamita granulosa	*Liquidambar orientalis* Mill., sap	180	Europe
Radix Mei athamantici	*Meum athamanticum* Jacq, root	180	Europe
Semen Amomi	*Elettaria cardamomum* (L.) Maton, seed	180	Asia
Nardus Celtica	*Valeriana celtica* L., root	180	Europe
Terra Lemnia vera	Medicinal earth	180	Europe
Phu ponticum	*Valeriana officinalis* L., herb	180	Europe
Chamaedrys	*Teucrium chamaedrys* L., herb	180	Europe
Folium, loco eius Macis et Gariophyllorum ana partes aequales	*Cinnamomum tamala* (Buch.-Ham.) T.Nees & Eberm., leaf (substitute: equal parts of *Myristica fragrans* Houtt., seed aril and *Syzygium aromaticum* (L.) Merr. & L.M.Perry, flower bud)	180	Asia
Chalcitis tosta	Iron(II) sulfate, anhydrous	180	Europe
Radix Gentianae	*Gentiana lutea* L., root	180	Europe
Semen Anisi electi	*Pimpinella anisum* L., fruit	180	Europe
Hypocystis	*Cytinus hypocystis* (L.) L., inflorescence	180	Europe
Cubeba	*Piper cubeba* L.f., fruit	180	Asia
Gummi Arabicum splendissimum	*Acacia* senega (L.) Willd.l, gum	180	Africa
Semen Foeniculi	*Foeniculum vulgare* Mill., fruit	180	Europe
Cardamomum	*Aframomum melegueta* K.Schum., seed	180	Asia
Seseli	*Seseli tortuosum* L., fruit	180	Europe
Succus Acaciae	*Acacia catechu* (L.f.) Willd., dried aqueous extract	180	Africa

(*continued on next page*)

Table 2 (*continued*)

Original name	Identification	Calculated quantity [g]	Origin[a]
Semen Thlaspios, loco eius Erucae	*Thlaspi arvense* L., seed (substitute: *Sinapis alba* L., seed)	180	Europe
Coma vel Flos Hyperici	*Hypericum perforatum* L., leaves and flowers	180	Europe
Semen Ameos	*Trachyspermum ammi* (L.) Sprague, fruit	180	Asia
Calamus aromaticus	*Acorus calamus* L., rhizome	180	Asia[b]
Grana Sagapeni	*Ferula persica* Willd., oleoresin	180	Europe
6 Class			
Castoreum Ponticum	*Castor fiber* L., castor sac content	90	Europe
Aristolochia longa	*Aristolochia rotunda* L. or *A. fontanesi* Boiss. & Reut., rhizome	90	Europe
Semen Dauci Cretici	*Athamanta cretensis* L., fruit	90	Europe
Bitumen Judaicum	Natural bitumen	90	Asia
Gummi Opopanacis	*Opopanax chironium* Koch, gummiresin	90	Europe
Flos Centaurii minoris	*Centaurium erythraea* Rafn, flower	90	Europe
Grana Galbani	*Ferula gummosa* Boiss., gummiresin	90	Europe
7 Class			
Mel despumatum	Honey, skimmed	62470	Europe

[a] In case of plants, species found in the vicinity of the Mediterranean Sea were treated as European.
[b] In the 17th c. *Acorus calamus* L. was not yet a part of the European flora.

2.2. Identification of contemporary scientific names of the theriac compounds

The identification of the names of compounds listed in the Theriac recipe by Guldenius was carried as follows: the list of the ingredients in the form initially written in the source was independently translated into the contemporary scientific Latin naming by each member of our team (two historians and two pharmacists). The basis of the identification were European scientific prints from the 16th to 18th c., like herbaries (Siennik, 1568), dispensatiories (Cordo, 1562), lexicons (Zedler, 1731) and similar sources. As supplementary sources were treated 19th c. lexicons (Wiorogórski and Zajączkowski, 1892–1918). The results were compared to the present scientific papers summing up the information about pre-Linnean naming of species in East-Central Europe (Bacler and Drobnik, 2009; Drobnik, 2015). The independently translated names were subsequently compared. In case of non-compliance, further literature on the subject was sought, until the translation was accepted unanimously. The translated names are presented in Tables 2 and 3. In the translation the then trade terms (e.g. *electus*, *massiliense*) were omitted.

3. Results and discussion

3.1. The manufacturer and credibility of his knowledge and skills

Paul Guldenius (Głowacki, 1953) (born in 1588) passed through apothecary training within a guild structure. In 1608, he took an apprenticeship journey to Wittenberg, which at the time was an important centre of Theriac production. There, at the University, he audited pharmacy courses and publicly prepared two Theriac formulations. For his excellent performance, the University Medical College granted him the license to manufacture *Theriacum Andromachi*. Then he settled down in Thorn, where during the plague outbreak in 1629 he developed the particular prescription for the medicine *in usum et commodum Reipublicae Thoruniensis* (for use and profit of the republic of Thorn) which he published a mere year later (Fig. 1). Shortly thereafter, he manufactured the Theriac in public, which took five days with much pomp and ceremony. In 1633, the local city council issued a testimony to the apothecary to confirm his skills and certify the quality of the medicine.

3.2. Value and use of theriac

In the early modern period Theriac was used against poisonings as well as against infectious diseases, first and foremost bubonic plague. Although to the modern scholars the two presented health issues are of a different aetiology, to the back-then science, dominated by humoral pathology, they were related. The humoral doctrine, based on the views attributed as far back as to Hippocrates (5th/4th c. BC), assumed the existence in body of four basic substances called the humors (Nutton, 1993). Disturbance of their balance or having them spoiled would cause disease.

The humoral physicians supposed that both for epidemic and intoxication the real cause was a "venom", entering into body and corrupting its liquids (Powodowski, 1589). Hence, drugs believed to neutralize poisons, such as Theriac, were used when a "venom" was diagnosed. Therefore early modern medics recommended the treacle to be used in case of epidemics (when the toxin was considered e.g. airborne) as well as after poisoning, a snake or a rabid dog bite etc. (Collard, 2013; Grévin, 1568; Platter, 1976)

Contemporaries actually believed that Theriac is a potent anti-epidemic drug. After all, it was used not only during the outbreaks of bubonic plague, the early modern epidemic disease par excellence. For instance, in 1551, during the sudor anglicus outbreak, numerous English physicians regarded the treacle as a staple in prophylaxis, cure and treatment of that mysterious and contagious disease (Watson, 1966). In the 17th c., London physicians assumed that Theriac might resist measles outbreaks among children and young adolescents (Salmon, 1682). Whereas in German-speaking territories in the 18th c. the treacle was used as a medicine against numerous types of "typhoid fevers" and typhus (Ger. Flecken-Fieber) (Bucholtz, 1772), smallpox (Hildebrandt, 1788) and other contagious diseases, including the cattle plague (Anonymous, 1745). In Muslim world, in turn, it was widely recommended during the outbreaks of cholera (Aleem et al., 2020).

Moreover, according to the physicians of the time, Theriac was a potent drug that should be prescribed only with the greatest precaution, and had significant contraindications, among which the most important was fever (Karamanou and Androutsos, 2019). Also, the effects of misuse were expected to be possibly fatal (Karamanou and Androutsos, 2019).

In early modern period, the treacle was undoubtedly one of the most expensive drugs. For instance, in 1625, in Thorn a drachm (also spelled "dram"; about 3.73 g) of Theriac Andromachi cost four silver groschen. The same applies to Danzig (present-day Gdańsk). Also in local pharmacies, in 1668, the drug fetched four groschen per drachm, whereas the same quantity of Theriac Diatesseron (Theriac for the poor) was four times cheaper. For an average man, a day labourer, this was a considerable price as by that time in Polish Prussia it was an equivalent of about 5 kg of wheat, whereas a chicken cost about three groschen and a goose about six (Anonymous, 1652). Moreover, it should be remembered that this was the price of a single dose, and the medicament was supposed to be taken in repeated doses.

Table 3
The combined preparations included in the Guldenius Theriac recipe, according to the Cordus Dispensatory (Cordo, 1562).

Original name	Identification	Calculated quantity[a] [g]	Origin
Trochisci Scillitici			
Scylla assata	*Drimia maritima* (L.) Stearn, baked bulb	1298	Europe
Farina Orobi	*Vicia ervilia* (L.) Willd., ground seed	865	Europe
Trochisci de Viperis			
Caro Viperinae cum Anetho, sale et aqua cocta	*Vipera berus* L., flesh boiled with *Anethum graveolens* L., herb and common salt	866	Europe
Panis triticeus purissimus tritus et cribratus	Wheat bread, dried and crumbled	216	Europe
Trochisci Hedichroi			
Marum sive Majorana, aut loco eius Dictamnus creticus	*Teucrium marum* L., herb (substitute: *Origanum majorana* L., herb or *Cistus creticus* L., leaf)	37.5	Europe
Asarum	*Asarum europaeum* L., root	37.5	Europe
Samsuchus	*Origanum majorana* L., herb	37.5	Europe
Aspalathus, eius loco sumatur Semen Agni casti	unspecified fragrant Indian wood[b] (substitute: *Vitex agnus castus* L., fruit)	37.5	Asia
Opobalsamum, eius loco accipiatur Oleum Charyophillorum	*Commiphora gileadensis* (L.) C.Chr., sap (substitute: *Syzygium aromaticum* (L.) Merr. & L.M.Perry, volatile oil)	37.5	Africa
Schoenanthus	*Cymbopogon schoenanthus* (L.) Spreng., herb	37.5	Africa
Calmus aromaticus, eius loco Galanga	*Acorus calamus* L., rhizome (substitute: *Alpinia galanga* (L.) Willd., rhizome)	37.5	Asia
Phu ponticum	*Valeriana officinalis* L., herb	37.5	Europe
Xylobalsamum	*Commiphora gileadensis* (L.) C.Chr., wood	45	Africa
Cinnamomum	*Cinnamomum verum* J.Presl, bark	45	Asia
Costus	*Saussurea costus* (Falc.) Lipsch., root	45	Asia
Mirrha Troglodytica	*Commiphora myrrha* (Nees) Engl., oleoresin	113.5	Africa
Folium aut succedaneum eius	*Cinnamomum tamala* (Buch.-Ham.) T.Nees & Eberm., leaf (or substitute)	113.5	Asia
Spica nardi Indicae	*Nardostachys jatamansi* (D. Don) DC., root	113.5	Asia
Crocus	*Crocus sativus* L., stigma	113.5	Europe
Cassia	*Cinnamomum cassia* (L.) J. Presl, bark	113.5	Asia
Amomum aut succedaneum eius	*Elettaria cardamomum* (L.) Maton, seed (or a substitute)	25.5	Asia
Mastix	*Pistacia lentiscus* L., resin	52.5	Europe
Vinum veteris odoratum dulcis, quantum satis	Old sweet wine with a strong aroma	just enough	Europe

[a] The quantity was calculated to match the Guldenius recipe.
[b] Comparing historical sources (Cordo, 1562; Zedler, 1731) most likely *Aspalathus* was a determination error rather than a specific species.

Basing on the historical sources it may be assumed that the average amount of Theriac taken as a single dose was usually no more than a few grams. Up to the 18th c., determining the correct dosage varied from patient to patient and always required in-depth experience of a medical practitioner (Rankin, 2021). The Medieval French physician, Bernard de Gordon, noted that the administration of three drachms at a time (about 11.3 g) was a severe overdose, with one drachm being the right quantity (Karamanou and Androutsos, 2019). In turn, the 17th c. guide with anti-epidemic instructions suggested a single dose to be the size of a pea (Petrycy, 1613). Therefore, the historical medical books do not support the assumptions about excessive use of the treacle because of narcotic properties (Karaberopoulos et al., 2012; Karamanou and Androutsos, 2019). One should also keep in mind that in the Early Modern Era opium was included in many preparations – in Cordus Dispensatory alone there is a separate chapter with 28 "sweetened drugs containing opium" (*Confectiones opiatae* (Cordo, 1562) – among them Theriac), with some recipes much less complex and supposedly cheaper than the treacle. Thus, given the information above and regarding that at the time pure opium was commercially available without any legal restrictions, it is highly unlikely that Theriac would be the preparation of first choice for recreational use.

3.3. The Guldenius theriac recipe

In the 16th–18th c. Theriac was being widely disputed (Tidicaeus, 1607), but most of the altered versions of the recipe were intended to be strictly theoretical and did not end up in the production stage. Therefore, in order to obtain reliable information on the possible pharmacological effect of the drug, the Authors needed to select the recipe that was actually produced. The Guldenius recipe was published and officially adopted by the city council of Thorn, who confirmed the authenticity and the fact that this version of the recipe was used.

The Guldenius recipe consisted of 61 individual compounds (two animal-, two mineral- and 57 plant-derived) and three combined preparations, divided into classes according to weight (Fig. 1, Table 2). The recipes for the combined preparations were taken from Cordus Dispensatory, the most widespread apothecary print of the time. They included further 11 compounds (one animal- and ten plant-derived – collected in Table 3), which made together 72 individual ingredients of the Theriac.

The translation of original names into the modern scientific language was in many cases captious, not only because of the pre-Linnean nomenclature in the Guldenius document, but also in terms of included apothecary common names. As an exemplary difficulty may serve the name Cardamomum (Table 2), that may be intuitively identified as the contemporary true cardamom. However, a thorough examination of then herbaries (Bauhin, 1651) revealed, that in Europe at the time this name was used for a different plant, *Aframomum melegueta* K.Schum. (Ger. Paradieskörner). The true cardamom, though, was also a part of the Theriac recipe, under the name Sem. Amomi. Interestingly, the same name (Sem. Amomi) about a century later started being used for allspice. The example shows how important it is to take into consideration all the historical and geographical dependencies. The collective work of the historical and pharmaceutical team made it possible to maintain within the context throughout the whole translation process. This is in accordance with the most recent suggestions for building the history of medicine research teams (Duma et al., 2021).

The Guldenius recipe contains two compounds that may be possibly toxic and, according to history-of-medicine researchers (Ahnfelt and Fors, 2016; Karaberopoulos et al., 2012), were supposed to be responsible for the pharmacological effect of the drug: opium and sea squill (Table 2 and Table 3, respectively). Yet, referring to the Paracelsian "The dose makes the poison", the sole presence of the mentioned substances does not imply a toxic effect to a patient. Assuming that opium contained about 10% of morphine (standard by the 10th European Pharmacopoeia) the calculated amount of the alkaloid in the highest noted single dose (one drachm) was maximally 4.9 mg, half of the today usual single dose for oral morphine solution taken as a painkiller. The calculation does not take into account possible interactions with other compounds or degradation during the preparation process. Regarding the pharmacological information, the use of Theriac as a recreational drug is thus highly unlikely, as the noted daily recreational oral doses of opium are estimated about 2 g (which corresponds to 200 mg of morphine) (Kramer, 1979), but an analgesic and anti-diarrhoeal effect could probably be observed. For the sea squill, which contains cardiac glycosides, the probability of being a toxic agent is even smaller. It was incorporated into Theriac as a processed baked bulb (*Scilla assata*) in the

Table 4
The constituents of the Guldenius Theriac recipe with anti-diarrhoeal compounds (Hegnauer, 1962–2001).

Recipe constituent	Anti-diarrhoeal compounds	Amount of constituent in a single dose [g]
Acacia catechu (L.f.) Willd., dried aqueous extract	catechins, tannins	0.008
Ajuga chamaepitys (L.) Schreb., herb	tannins	0.008
Cinnamomum cassia (L.) J.Presl, bark	tannins	0.016
Cinnamomum verum J.Presl, bark	tannins	0.026
Cistus creticus L., hairless leaf	tannins	0.011
Clinopodium nepeta (L.) Kuntze, herb	tannins	0.011
Cytinus hypocystis (L.) L., inflorescence	tannins	0.008
Lavandula stoechas L., flower	tannins	0.011
Marrubium vulgare L., shoot top	tannins	0.011
Origanum majorana L., herb	tannins	0.002
Papaver somniferum L., latex	opiate alkaloids	0.049
Potentilla reptans L., rhizome	tannins	0.011
Rheum palmatum L., root	tannins	0.011
Rosa spp., red petals	tannins	0.024
Teucrium chamaedrys L., herb	tannins	0.008
Teucrium marum L., herb (or substitute)	tannins	0.002
Teucrium montanum L., herb	tannins	0.008
Teucrium scordium L., leaves and flowers	tannins	0.024

calculated amount of 58 mg per single dose. The plant bulb, however, is reported to cause no intoxication even in doses exceeding 3 g (Mahboubi et al., 2019). The other compounds of the Guldenius Theriac do not exhibit toxic properties, according to the literature data. Thus, the calculations show that most likely no poisoning could result from Theriac, when taken as prescribed.

The recipe also includes many plant substances that are used in modern phytotherapy and are recommended by the European Medicines Agency (EMA) (Herbal Medicinal Product Committee, 2017), either because of the well-established use (like ginger, St. John's wort, rheum or valerian) or due to traditional use (like liquorice, anise, fennel or great yellow gentian). Yet, due to a large number of compounds, each one of them is included in the single dose of treacle in an amount far below the therapeutic level. For example, EMA suggests a single dose of ginger to be 1 g of the powdered substance, while in the calculated single dose of Theriac there are only 11 mg included. The same observation also applies to the other herbs. The largest part of the single dose is honey (2.82 g). Still, there is a possible synergy regarding the anti-diarrhoeal effect. There are two classes of compounds that exhibit this activity: opiate alkaloids and tannins (present i.e. in cortices, radices, rhizomes and several herbs; Table 4). The amount of opium in a single dose resembles the modern anti-diarrhoeal dosage. Tannins from different chemical classes were present in 200 mg of plant materials in a single dose, which is below the therapeutic level of tannic compounds (estimated at 2 g), as suggested by EMA for *Tormentillae rhizoma*, the exemplary tannic anti-diarrhoeal herb (Herbal Medicinal Product Committee, 2017). However, both classes act with different mechanism and even though a complexation between the two classes occurs to some extent, the anti-diarrhoeal effect may be expected with a reasonable probability. In case of rheum, which is a known laxative, it should be noted that 11 mg of the substance in a single dose (which corresponds to 0.2 mg of anthranoids) is far below the active dose and thus only tannins from the herb are contributing in overall anti-diarrhoeal activity. The results are consistent with historical sources: the Islamic pharmacopoeia by al-Biruni (about 10th c.) mentioned the anti-diarrhoeal activity as a confirmation of Theriac quality (Aleem et al., 2020; Nappi, 2009).

The vast majority of the Theriac compounds may be described as aromatic. Medics from the Early Modern period particularly valued spicy and pungent plants which were supposed to dry and heat the body, thus removing particularly dangerous wet and cold humors (considered responsible for many diseases) (Conrad et al., 1995). The exact mechanism was the cause for which the treacle was seen as dangerous in case of fevers. Moreover, hot and spicy tasting substances were expected to have the ability to burn up venoms and toxins inside the body (Petrycy, 1613), which was the ground for Theriac anticipated anti-epidemic and anti-poisonous activity. Therefore, it can be seen that the composition of Theriac as well as its indications and contraindications were in full accordance with the scientific opinions of the time.

One of the most frequently mentioned compounds of Theriac is viper flesh. It attracts attention from Antiquity, mainly because is derived from a poisonous reptile. Yet, *carnis viperinae* was widely used by physicians and apothecaries not only as an ingredient of the treacle. For instance, Crateuas, the personal physician of Mithridates VI, used the flesh of the viper in leprous patients (Hunt, 2020). The Roman medic Antonius Musa claimed to cure with it the otherwise incurable ulcers (Shaw, 1802). Hippocrates prescribed broth of vipers against lichen, whereas Galen recommended it against elephantiasis (McKenzie, 1927). As early as the mid-17th century, the opinion on viper flesh as a potent medicinal remedy was well-established among physicians and apothecaries from all over Europe (Panicelli, 1630). It was prescribed for numerous disorders starting with tumors, and ending with childbirth pains (McDonald, 1994). Moreover, it was highly esteemed, especially in France and Italy, as a restorative medicine (Stephenson, 1832). Likewise, viper's and snakes' flesh was used as a remedy in the Islamic World (Elgood, 1951), Africa, and India (Shaw, 1802), and has been a part of traditional resp. folk medicine, e.g. in Poland (Chętnik, 1971), Uzbekistan (Akbarov et al., 2020), and Portugal (Alves and Rosa, 2012).

The reason for including the viper's flesh into the treacle was the opinion shared also by Galen and his contemporaries, that it is medicinal against poison because it was believed to have strong drying and burning properties, which would even cause a person who ate the flesh to develop a fever and unquenchable thirst (Leigh, 2016). Hence, due to its putative anti-poisonous activity, viper flesh was considered one of the crucial Theriac compounds up to the 19th c. (Griffin, 2004).

Most of the compounds included in the whole recipe are of European origin (47, Tables 2–3), while 18 were imported from Asia, and seven from Africa, which is another confirmation of the resilience of intercontinental trade at that time, although for some hardly available materials, Guldenius suggested substitutions. Even the European ingredients, though, in the vast majority had to be imported to Thorn, as only few of the European species are abundant in the indigenous flora, e. g. St. John's wort, creeping cinquefoil or field pennycress. Still, it is not a proof that the native ones were actually collected locally. Moreover, for some other compounds, like *Castoreum ponticum*, the trade name (*ponticum*) suggests that the component was brought from abroad, even though the source species (European beaver) was domestic. This was one of the factors increasing the price of the drug.

4. Conclusions

Summing up the results, due to the extreme complexity of the Theriac recipe after theoretical analysis it is easier to say what pharmacological effect the medicine did not have than what it actually had. Historical and phytochemical investigations have consistently shown that – at least in the Early Modern period – the assumptions regarding narcotic or toxic effects of Theriac are not supported by the results. On the other hand, taking into account the compounds one can expect positive results in antioxidant tests or antimicrobial and anti-inflammatory activity. Still, at the moment there is no indication that the famous panacea's efficacy in the main indications was based on anything more than just a placebo effect. Was it a quackery, then? No, as the composition was in accordance with the humoral medicine and patient's trust was strictly then-science-based. Nevertheless, the theoretical estimates regarding the real pharmacological activity of Theriac carry a risk of error as some impossible to predict synergies may occur in the matrix that complex. The confirmation can be only achieved after a piece of the actual Theriac is reconstructed respecting the back-then methodology, and subsequently subjected to modern tests and analyses.

CRediT authorship contribution statement

Danuta Raj: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Katarzyna Pękacka-Falkowska:** Methodology, Investigation, Writing – original draft, Writing – review & editing. **Maciej Włodarczyk:** Investigation, Writing – original draft, Writing – review & editing, Visualization. **Jakub Węglorz:** Methodology, Investigation, Writing – original draft, Writing – review & editing, Funding acquisition.

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