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The rise and fall of mandrake in medicine*

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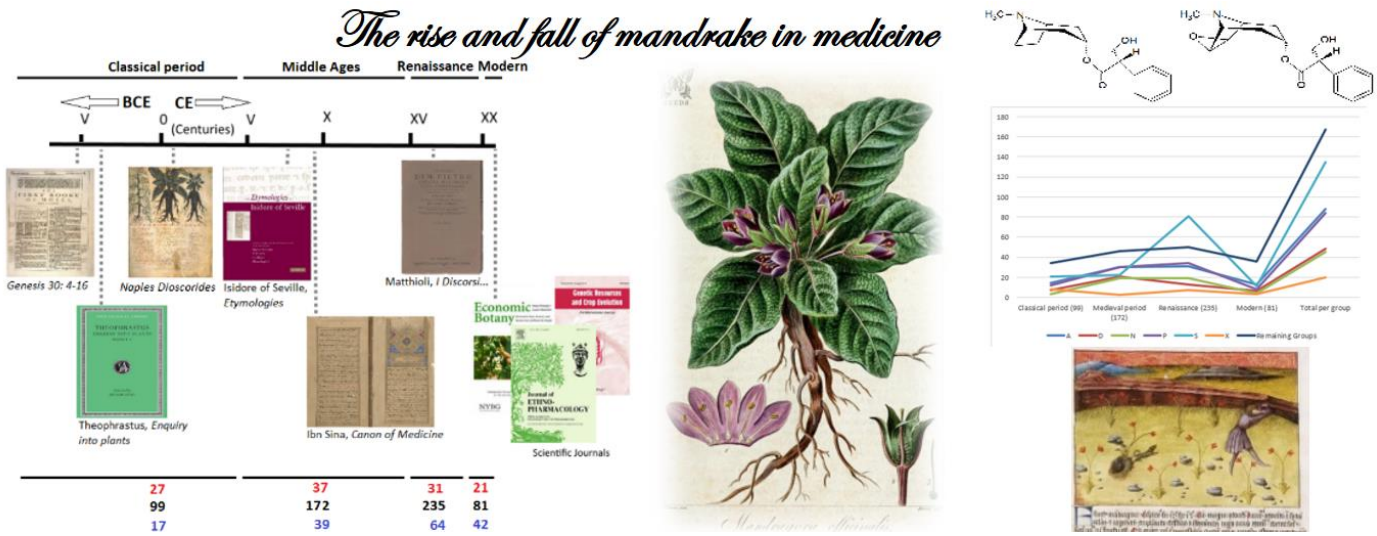

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Abbreviations: URs: Use records; N: North; S: South; E: East; W: West; A: General and unspecified; B: Blood, blood forming organs and immune mechanism; D: Digestive; F: Eye; H: Ear; K: Cardiovascular; L: Musculoskeletal; N: Neurological; P: Psychological; R: Respiratory; S: Skin; T: Endocrine, metabolic and nutritional; U: Urological; W: Pregnancy, childbearing, family planning; X: Female genital; Y: Male genital; Z: Social problems.

*Cleopatra: "*ha, ha! Give me to drink mandragora. That I might sleep out this great gap of time. My Antony is away*." (Shakespeare [1564-1616], Antony and Cleopatra, Act I., scene V, 4/5.

Index

Abstract

Ethnopharmacological relevance: Mandrake (*Mandragora* sp.) is one of the most famous medicinal plants. It has been in continuous medical use throughout written history and is still in use today in popular medicine.

Aim of the study: Mandrake derived drugs once played an important role in medicine and in magical practices. Today, the role of mandrake in popular medicine is marginal. However, natural products present in mandrake such as atropine and scopolamine, as well as their semi synthetic derivatives continue to hold and important role in medicine. Here we aim to trace the development of historical rationales and scientific events that led to the abandonment of mandrake as a medicine.

Materials and Methods: We review the medicinal uses of mandrake drugs since antiquity in an attempt to pinpoint use patterns that were popular in certain periods of time and others that are more general. We compare the uses from the native territories to those from regions where the plant got introduced and use literature reporting mandrake's chemistry and pharmacology in order to explain the diachronic changes of use patterns.

Results and Conclusion: We found information about 88 different medicinal uses for mandrake, grouped into 39 conditions. According to the number of different medicinal uses, the most versatile period was the medieval (37), followed by the Renaissance (31), the classical (27), and the modern period (21). Considering the higher number of textual sources and use-records collected for the Renaissance period, the decrease of versatility in comparison to the medieval period appears robust. This seems to indicate a more consolidated use pattern, that might be conditioned by the reproduction of classic textual sources as well as by a less experimental approach and reduced popularity of mandrake in medicine. The introduction of the volatile anaesthetics with more reliable narcotic effects set the seal on using mandrake in surgery but opened the way for atropine being used as a prophylactic and antidote during surgical interventions.

Keywords: diachronic medicinal plant use, history, herbals, *Mandragora*, ethnobotany

1 Introduction

Mandrake (*Mandragora* sp., Solanaceae) is one of the most famous medicinal plants of the Mediterranean and Europe (Randolph, 1905; Dumas, 1932, p. 6; Thompson, 1934; Keezer, 1963, p. 189). Its avenue to fame and popularity was paved by legends such as the deadly effect the plant would have on those who dig it up, wherefore it had been said that a dog should be used to complete the root-digger's job (Frazer, 1917). This story, that can be found in Josephus Flavius' Jewish Wars (VII, 183-184) (Matthioli, 1568; Frazer, 1917) together with the identification of mandrake fruits as the aphrodisiac and fertility enhancing 'love-apples' (*Dūdāʾīm*) in the Old Testament (Genesis 30:14; Randolph, 1905; Frazer, 1917) found their way into world literature. Mandrake is mentioned in Shakespeare's 'Romeo and Juliet', in Machiavelli's 'La Mandragora', Samuel Becketts's 'Waiting for Godot' and Rowling's 'Harry Potter and the Chamber of Secrets'.

The etymology of the Hebrew *dūdāʾīm* (דודאים) is not entirely clear but seems to derive from '*dwd*' (= to love) or '*dod*' meaning 'passion', 'carnal love' or 'beloved' (Felix, 1957; Fleisher and Fleisher, 1994). *Dūdāʾīm* was translated as "love producing" by Harrison (1956) and is phonetically similar to the Hebrew word for 'two lovers' or 'couple in love' (Felix, 1957). Most scholars agree that *dūdāʾīm* mentioned in Genesis 30:14 corresponds to fruits of mandrake (Frazer, 1917; Amar, 2012; Dafni and Böck, 2019) and that the fruits with allegedly aphrodisiac and fertility promoting properties found by Ruben on the fields during the time of the wheat harvest, thus in May, correspond to mandrake berries. However, Preuss (1971, p. 539–540) and Zohary (1982) have some reservations. The only part of the plant that is edible is in fact the fruit exempt from the relatively large seeds (Crowfoot and Baldensperger, 1932; Al-Khalil and Alkofahi, 1996; Ungricht et al., 1998; Hanuš et al., 2006). Gerard (1597, p. 282) specified that the fruits ("apples") are milder than the root and that it was "reported that they may be eaten, being boiled with pepper and other hot

spices". The rest of the plant, including the seeds, contain anticholinergic tropane alkaloids such as scopolamine and L-hyoscyamine with a relatively low therapeutic index (Hanuš et al., 2005; Goodman, 2010).

Although there are written artefacts of its possible use in ancient Mesopotamia and Egypt (see below), we consider the oldest reliable textual source of a medicinal use of mandrake to be the Old Testament (Genesis, 30:14), mentioning its fruits as an aphrodisiac. Mandrake was described in the *Corpus Hippocraticum* (see below) and in Theophrastus' *Historia plantarum* (IX, 9.1) (c. 372/371–287/286 BCE; Sollenberger, 2008) and in the following discussed by almost all commentators on *materia medica*. Mandrake's chemistry has been elucidated and the pharmacology of its main metabolites investigated but a diachronic analysis of the documented uses of its various drugs has not been conducted so far.

1.1 Taxonomy and ethnotaxonomy of *Mandragora* sp.

The genus *Mandragora* L. (Solanaceae) was established by Tournefort (1700) and later validated by Linnæus (1753), with *M. officinarum* L., as a single species. However, since antiquity, a male (Greek: *mandragóras árrēn*, Latin: *mandragoras mas* or *mandragoras masculus*) and a female (Greek: *Mandragóras thêlis*, Latin: *Mandragoras foemina*) mandrake have been distinguished. Dioscorides (Matthioli, 1568, Jackson and Berry, 1979) and Pliny the Elder (23–79 CE; 'Natural History', Book XXV) reported that the male mandrake was also called 'white' and the female 'black' mandrake, according to the colour of the roots. Also, pre-Linnean botanists distinguished two types of mandrakes, such as e.g., Bauhin (1623), who identified *Mandragora fructo pyri* and *Mandragora flore subcaeruleo purpurascente*, or Parkinson (1629), who recognized a male mandrake with greenish-white flowers blooming in March and fruiting in July and a female mandrake with bluish-purple flowers appearing in August or September (Jackson and Berry, 1979; Ungricht et al., 1998). Sprengel (1824-1828) in his edition of Linnæus' *Systema Vegetabilium* validated two names suggested by Bertoloni, who used morphological and phenological differences to propose *M. vernalis* Bertol. and *M. autumnalis* Bertol., going against Linnæus' unified classification. However, the first name was considered superfluous as the classification being congruent with Linnæus' *M. officinarum* (Ungricht et al., 1998).

Based on the summary of phenological and morphological markers and ethnotaxonomies made by a range of scholars, the French botanist Tercinet associated mandrakes with pale violet flowers in October and November, ovoid berries, and roots with a blackish colour with the female mandrake or *Mandragora fructu pyri* and ultimately, with *M. autumnalis* (Jackson and Berry, 1979). Mandrakes with whitish-green to pale yellow flowers, flowering in March and April, with globose berries larger than those of *M. autumnalis*, with large and whitish roots were associated with the male mandrake or *Mandragora fructu rotundo* and thus *M. officinarum* (Jackson and Berry, 1979).

Due to the high morphological and phenological variability (see Ungricht et al., 1998) and in lack of molecular data sustaining two genetically and geographically distinct populations (Volis et al., 2015; 2018) currently both, Sprengel's (two species, *M. officinarum* (= *M. vernali*s) and *M. autumnalis*) and Linnæus' (*M. officinarum sensu lato*) classifications are accepted. The *Flora Europaea* (Hawkes, 1972), Kew's Medicinal Plant Names Services (Kew, 2021), and Kew's plantsoftheworldonline.org, list *M. officinarum* and *M. autumnalis*. The geographical distribution of *M. officinarum* would thus be mainland Italy, the territory of ex-Yugoslavia, Lebanon and Syria while the distribution of *M. autumnalis* would be Portugal, mainland Spain, the Balearic Islands, Sardinia, Sicily, southern Italy, Greece, Cyprus, the East Aegean islands, Turkey, Syria, Lebanon, Palestine, Iran, Tunisia, Algeria and Morocco (Hawkes, 1972; Valdés, 2012). In line with the *Flora Europaea*, most floras recognise two species (Gallego, 2012; Franco, 1984; Pignatti, 1982; Hawkes, 1972; Davis, 1978; Fennane et al., 2007; Le Floc´h et al., 2010; Feinbrun and Danin, 1991). On the other hand, authors and databases that accept *M. officinarum sensu lato* (following Ungricht et al., 1998) for all European, Mediterranean and Middle East *Mandragora* populations are Dobignard and Chatelain (2013), the African Plant Database (APD, 2012) and theplantlist.org. Accepted *Mandragora* species distributed outside this territory and thus, not considered in this review, are *M. turcomanica* Mizg. growing in Turkmenistan and Iran (Linczevsky, 1997, p. 67; Akhani and Ghorbani, 2003), and *M. caulescens* C.B. Clarke growing in China (Kuang and Lu, 1978).

2 Research question and rationale

The aim of this article is to trace the written history of mandrake and its rise and fall in medicine. In a diachronic analysis we compare the consensus of traditional uses of mandrake across time around the Mediterranean and Europe and contextualize the medical uses with phytochemical and pharmacological literature. The diachronic perspective permits to trace the evolution of therapeutic uses and associate changes of the therapeutic consensus with epidemiology and progress in pharmacology and medicine. The geographical analysis allows to comprehend the territorial extension of each use, and to detect possible differences of medicinal uses in areas where the plant is considered native *vs*. non-native areas. Although the approach depends on the availability of written texts and access to literature, we expect to see use patterns reflecting historical developments. Particularly, the turning away from using mandrake after the middle of the 13th century as an anaesthetic in surgery could not yet be explained satisfactorily (Scarborough, 2010).

3 Materials and Methods

3.1 General

A detailed literature search with the terms "*Mandragora*", "*Mandragora officinarum*", "*Mandragora autumnalis*" and "mandrake" in combination with "traditional use", "medicinal use", "chemical

compounds", "phytochemistry" and "pharmacology" was conducted using Scopus (Elsevier), Web of Science (Clarivate Analytics), Google Scholar and several digital libraries. Information was retrieved from herbal books, historical literature, doctoral theses and ethnobotanical literature. Historical texts were chosen according to their importance through one textual accession avoiding duplication of textual sources (e.g., herbals of the Middle Ages).

For transparency reasons we include the reference of the original author together with that of the translator or interpreter (e.g., Hippocrates, *Loc. Hom.* 39; Potter, 1995). We also added the original chapter and section whenever available, e.g., Pliny, Natural History 25, 150 (Bonet, 2014), or Dioscorides' *De Materia Medica* IV, 75.4 (Beck, 2017). Therapeutic recommendations and medical uses of mandrake (*M. officinarum* and *M. autumnalis*) derived herbal drugs across the Mediterranean basin, Europe and the Middle East, whether used as a single drug or as a component of drug mixtures, were considered and the botanical part accounted for whenever specified.

Before introducing and cultivating mandrake in Central and Northern Europe, only traded roots, that were often faked or adulterated (e.g., substituted with the root of *Bryonia* sp., Cucurbitaceae; see e.g., Fuchs, 1543 Chap. CCI), were available in these regions. Therefore, we distinguish use data from regions where the plant is native, from use data reported from non-native regions in order, to account for differences conditioned by cultural background and supply.

The phytochemical review of *Mandragora* sp. considers species, organs and the concentrations of the metabolites. A detailed list of the vernacular names given to mandrake in the various cultures and languages as well as its relation to the myths associated to the plant can be found in Dafni et al. (2021). Plant names throughout this paper are according to the MPNS (Medicinal Plant Names Services, KEW, 2021).

The ethnopharmacological review is based on an interdisciplinary pharmacognostic comparison including the consensus between traditional and allopathic medicine (Leonti and Weckerle, 2015). This entails a discussion and explanation of selected traditional uses in light of phytochemical and pharmacological literature data for those uses and conditions for which such a discussion is meaningful.

3.2 Standardization of citations and therapeutic uses

The reported medical uses for mandrake derived botanical drugs were classified according to the 17 health care chapters (use groups) identified by the International Classification of Primary Care (ICPC-2; Staub et al., 2015). ICPC-2 distinguishes: A: General and unspecified; B: Blood, blood forming organs and immune mechanism; D: Digestive; F: Eye; H: Ear; K: Cardiovascular; L: Musculoskeletal; N: Neurological; P: Psychological; R: Respiratory; S: Skin; T: Endocrine, metabolic and nutritional; U: Urological; W: Pregnancy, childbearing, family planning; X: Female genital; Y: Male genital; Z: Social problems. As an exception to the ICPC-2, toothache was classified under A01 (Pain general/multiple sites) and not under

D19 (Teeth/gum symptom/complaint). We classified anaesthetic uses under A01 but arranging them in a separate row (Appendix A). The “acute, fever producing disease characterized by diffusely spreading deep-red inflammation of the skin or mucuous membranes” associated with pustules and mentioned by Ibn Sina (2012, p. 701) was interpreted and classified as escarlatte. Mentions of intoxicating effects including ‘narcotic’ or ‘hallucinogenic’ as well as uses as a poison (e.g., “to kill”) were grouped together in a separate and additional category to the ICPC-2 categories. The classification of conditions and symptoms into the different use groups is shown in Table 1 and Appendix A together with all textual sources and quotes mentioning uses of *Mandragora* sp. derived drugs.

3.3 Data analysis, diachronic and geographical analysis

Data used for the diachronic and geographical analysis were compiled in Microsoft Excel. For the analysis, data were arranged into four time periods (1a-1d) and two geographical regions (2a and 2b). The distinguished time periods are 1a: Classical period (4th century BCE up to the 4th century- CE); 1b: Medieval period (or Middle Ages: 5th century–1492); 1c: Renaissance period (with 19th century; 1492-1899) and 1d: Modern era (1900 onwards).

The two geographical regions are 2a (*Mandragora* sp. is native): Southern Europe; Turkey; Israel, Jordan, Syria, Lebanon, Palestine (The Middle East); Tunisia, Algeria and Morocco (North Africa) and 2b (*Mandragora* sp. is not native): Western, Central and Northern Europe, Iran, Iraq, Serbia, Croatia (the plant is not endemic according to Flora Croatica Database, 2022), Armenia, Egypt and Arabia (see introduction for further details).

3.4 Ancient Mesopotamia and Egypt – data excluded from the analysis

Written information about mandrake’s medicinal properties may date back to ancient Mesopotamia (c.f. Thompson, 1924, 1926); however, the identification is not clear at all (Böck, 2021). *Mandragora* sp. is not native to Mesopotamia and Egypt which puts the identification of mandrake based on ancient Egyptian written sources in doubt (Germer, 2008) in spite of explicit iconographic depictions (see Bosse-Griffiths, 2001).

Thus, medicinal uses that have been ascribed to mandrake from the ancient Mesopotamian and Egyptian period have been excluded from the analysis. This includes the treatment of wounded feet (Thompson, 1923, no. 73,1 ii:27), as an emetic (Köcher, 1980, no. 575 i:44), against toothache, to ease delivery, problems of the anus such as haemorrhoids (Köcher, 1963, no. 1 l. 11 and 248 iv:19), and to treat stiff hips and as an amulet to ward off snake bites (Gurney and Finkelstein, 1957, no. 92 i:9).

4 Results and discussion

4.1 Considered literature

The considered literature spans the time of the translation of the Hebrew Bible into the Greek Septuagint around 250 BCE until now including 153 different textual sources. Uses from the classical period (4th century BCE - 4th century CE) were sourced from 17 different texts and are related to 27 original authors (as several texts include information from more than one author (e.g., Keyser and Irby-Massie, 2008). Besides the already mentioned Dioscorides, Pliny, Hippocrates and Theophrastus we found information by Aristoteles (Aristoklēs, 384 – 322 BCE), Galen (129 – c. 216 CE), Celsus (Cornelius Celsus, 15-35 CE), and other lesser-known authors such as Philoxenus (Greek writer, 1st cent. BCE; see Keyser and Irby-Massie, 2008 for a detailed list of ancient Greek authors citing mandrake). Thirty-nine written sources were considered for the medieval period, including the 'Cannon of Medicine' by Ibn Sina, the Cairo Geniza (Lev, 2007), Maimonides' 'Poisons and their Antidotes' (Muntner & ben Maimon, 1942), and the Lorsch pharmacopoeia (Stol, 1992). We considered 64 textual sources for the Renaissance period, including well-reputed authors like Fuchs (1542), or Gerard (1597) as well as translators and commentators of *De Materia Medica* like Matthioli (1568), Laguna (1555) or Linnaeus (1782). For the modern era, 42 sources, mostly academic papers reporting on ethnobotanical uses, were retrieved (Fig. 1 and Appendix A).

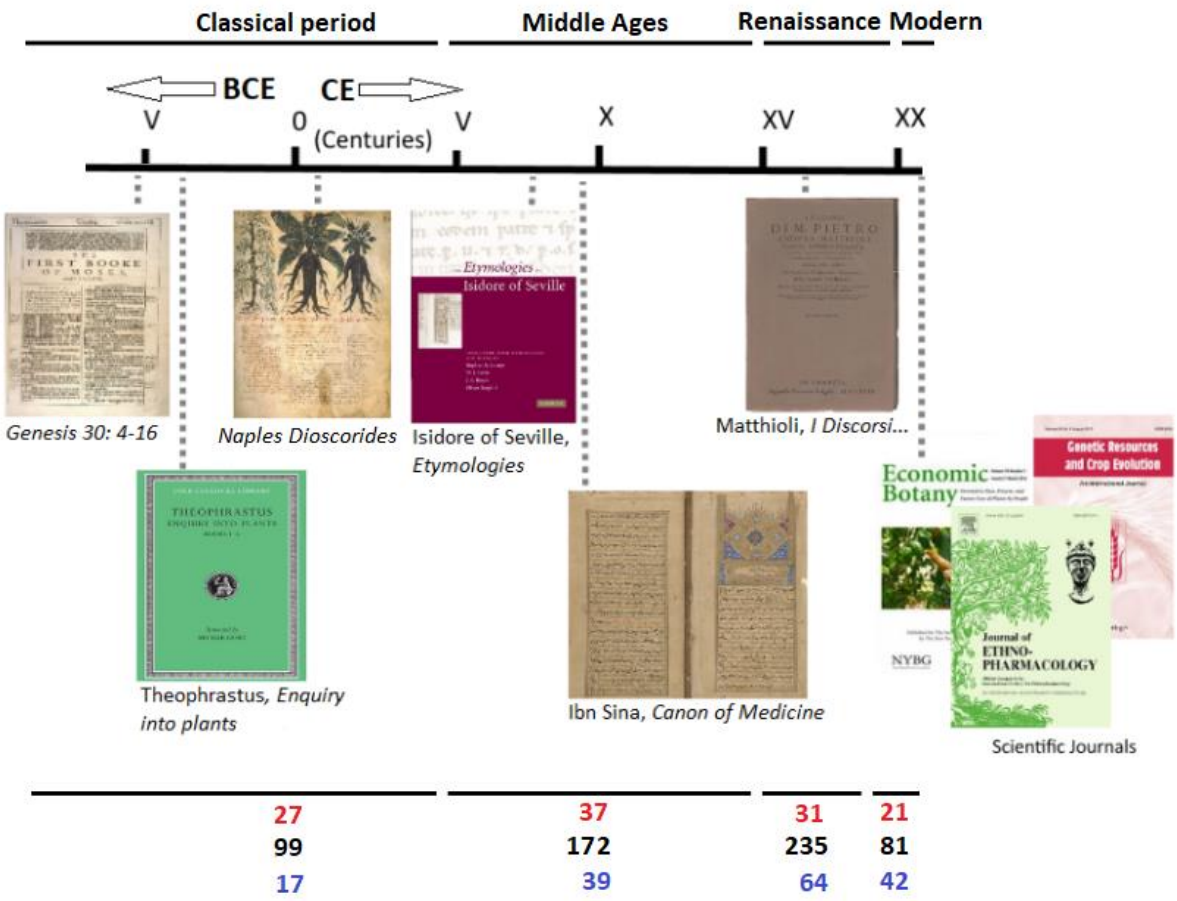

Figure 1. Timeline with some of the most important textual sources and the total number of medicinal uses (red), use-records (black) and considered written sources (blue) per time period.

4.2 Therapeutic uses of mandrake derived drugs

We collected 587 use-records (URs) arranged into ICPC groups, plus another 34 related to poisons and narcotic uses (Table 1). The 587 use-records are associated with 88 therapeutic uses that were organized into 39 conditions and arranged into 16 ICPC use groups. Skin problems (S; 135 records) was the ICPC use group with most use-records, followed by general and unspecified conditions (A; 88), psychological (P; 84), digestive (D; 48) and neurological conditions (N; 45). The most frequent therapeutic uses were for treating skin inflammations (68 URs), other skin problems (55 URs), to induce sleep (46 URs), for pain relief (42 URs) and to treat problems of the digestive tract (34 URs). The distribution of mandrake's therapeutic uses across time and use groups are presented in condensed form in Table 1 and in more detail in Appendix A.

Table 1. Medical uses of mandrake across historical periods. CP: Classical period; N: Native (S Europe, Israel, Jordan, Palestine and N Africa). NN: Non-native: Central/Western/Northern Europe, Iran, Iraq, Serbia, Croatia, Armenia, Egypt and Arabia. For details see Appendix A.

	CP	**Medieval**			**Renaissance**			**Modern**			**Total UR**	**Total N**	**Total NN**	**% N**
	N	**N**	**NN**	**SUM**	**N**	**NN**	**SUM**	**N**	**NN**	**SUM**				
Intoxicant use														
Toxic effect, Narcotic	8	4	-	4	4	12	16	6	-	6	34	22	12	64,7
Medicinal use (ICPC-2)														
A: Pain general	5	5	5	10	6	11	17	9	1	10	42	25	17	59,5
A: Anaesthetics	5	6	2	8	7	3	10	2	1	3	26	20	6	76,9
A: Fever	1	4	3	7	1	2	3	-	-	-	11	6	5	54,5
A: Poisoning / Antidote	2	-	3	3	2	-	2	-	-	-	7	4	3	57,1
A: Rabies	-	-	2	2	-	-	-	-	-	-	2	-	2	0,0
TOTAL of group A	**13**	**15**	**15**	**30**	**16**	**16**	**32**	**11**	**2**	**13**	**88**	**55**	**33**	**62,5**
B: Spleen	1	-	-	-	1	1	2	-	-	-	3	2	1	66,7
TOTAL of group B	**1**	**0**	**0**	**0**	**1**	**1**	**2**	**0**	**0**	**0**	**3**	**2**	**1**	**66,7**
D: Digestive symptoms	5	10	4	14	4	7	11	4	-	4	34	23	11	67,6
D: Teeth symptom	1	-	1	1	-	-	-	-	-	-	2	1	1	50,0
D: Stomach ulcer	-	1	2	3	-	-	-	1	-	1	4	2	2	50,0
D: Jaundice	-	1	-	1	-	-	-	-	-	-	1	1	-	100,0
D: Liver disease	2	2	-	2	2	-	2	1	-	1	7	7	-	100,0
TOTAL of group D	**8**	**14**	**8**	**22**	**6**	**6**	**12**	**6**	**0**	**6**	**48**	**34**	**14**	**70,8**

F: Eye symptoms / complaint	8	4	1	5	3	8	11	-	1	1	25	15	10	60,0
TOTAL of group F	**8**	**4**	**1**	**5**	**3**	**8**	**11**	**0**	**1**	**1**	**25**	**15**	**10**	**60,0**
H: Ear symptoms	-	3	4	7	1	-	1	-	-	-	8	4	4	50,0
TOTAL of group H	**0**	**3**	**4**	**7**	**1**	**0**	**1**	**0**	**0**	**0**	**8**	**4**	**4**	**50,0**
K: Irregular heartbeat	-	1	1	2	1	-	1	-	-	-	3	2	1	66,7
K: Hemorrhoids	1	-	1	1	-	-	-	4	-	4	6	5	1	83,3
TOTAL of group K	**1**	**1**	**2**	**3**	**1**	**0**	**1**	**4**	**0**	**4**	**9**	**7**	**2**	**77,8**
L: Rheumatism	6	4	6	10	3	1	4	7	1	8	28	20	8	71,4
L: Fracture	-	-	-	-	-	1	1	-	-	-	1	-	1	0,0
TOTALS of group L	**6**	**4**	**6**	**10**	**3**	**2**	**5**	**7**	**1**	**8**	**29**	**20**	**9**	**69,0**
N: Headache	1	3	5	8	3	5	8	1	1	2	19	8	11	42,1
N: Convulsions	2	2	2	4	2	2	4	1	1	2	12	7	5	58,3
N: Epilepsy	-	-	6	6	2	5	7	-	-	-	13	2	11	15,4
N: Paralysis	-	-	1	1	-	-	-	-	-	-	1	-	1	0,0
TOTAL of group N	**3**	**5**	**14**	**19**	**7**	**12**	**19**	**2**	**2**	**4**	**45**	**17**	**28**	**37,8**
P: Sleep disturbance	6	11	8	19	8	11	19	2	-	2	46	27	19	58,7
P: Feeling anxious / Sedative	2	3	-	3	1	1	2	5	-	5	12	11	1	91,7
P: Psychological symptoms / Depression	2	1	1	2	2	6	8	-	1	1	13	5	8	38,5
P: Psychological disorders /Madness	2	-	6	6	5	-	5	-	-	-	13	7	6	53,8
TOTAL of group P	**12**	**15**	**15**	**30**	**16**	**18**	**34**	**7**	**1**	**8**	**84**	**50**	**34**	**59,5**
R: Respiratory symptoms	3	3	1	4	-	1	1	4	-	4	12	10	2	83,3
R: Cough / Cold	2	2	2	4	-	2	2	4	-	4	12	8	4	66,7
R: Haemoptytis	3	-	2	2	1	-	1	-	-	-	6	4	2	66,7
R: Nose bleed	-	-	1	1	-	-	-	-	-	-	1	-	1	0,0
TOTALS of group R	**8**	**5**	**6**	**11**	**1**	**3**	**4**	**8**	**0**	**8**	**31**	**22**	**9**	**71,0**
S: Inflammation / Tumor	10	2	5	7	22	27	49	2	-	2	68	36	32	52,9
S: Skin problems	7	5	4	9	19	11	30	9	-	9	55	40	15	72,7
S: Animal bites	4	3	3	6	2	-	2	-	-	-	12	9	3	75,0
TOTAL of group S	**21**	**10**	**12**	**22**	**43**	**38**	**81**	**11**	**0**	**11**	**135**	**85**	**50**	**63,0**
T: Gout	3	1	3	3	2	5	7	-	-	-	13	6	8	46,2
T: Loss of appetite	-	1	-	1	-	-	-	3	-	3	4	4	-	100,0
TOTALS of group T	**3**	**2**	**3**	**4**	**2**	**5**	**7**	**3**	**0**	**3**	**17**	**10**	**8**	**58,8**
U: Urinary problems	-	1	1	2	1	2	3	2	-	2	7	4	3	57,1
TOTAL of group U	**0**	**1**	**1**	**2**	**1**	**2**	**3**	**2**	**0**	**2**	**7**	**4**	**3**	**57,1**
W: Abortion / Unwanted pregnancy	3	1	2	3	4	4	8	-	-	-	14	8	6	57,1
W: Subfertility / Aphrodisiac / Philtre	4	-	1	1	4	-	4	7	3	10	19	15	4	78,9
TOTAL of group W	**7**	**1**	**3**	**4**	**8**	**4**	**12**	**7**	**3**	**10**	**33**	**23**	**10**	**69,7**
X: Gynecology /Female troubles	8	1	1	2	2	5	7	2	1	3	20	13	7	65,0
TOTAL of group X	**8**	**1**	**1**	**2**	**2**	**5**	**7**	**2**	**1**	**3**	**20**	**13**	**7**	**65,0**
Y: Syphilis / Venereal diseases	-	1	-	1	-	4	4	-	-	-	5	1	4	20,0
TOTAL of group Y	**0**	**1**	**0**	**1**	**0**	**4**	**4**	**0**	**0**	**0**	**5**	**1**	**4**	**20,0**
TOTALS ALL GROUPS (Index of period´s peak use)	**99**	**82**	**91**	**172**	**111**	**124**	**235**	**70**	**11**	**81**	**587**	**362**	**225**	**61,8**

4.3 Traditional use of the different botanical drugs from *Mandragora* sp.

Remarkably, the textual sources distinguishing the different parts i.e., botanical drugs of mandrake are above all those belonging to the classic and the modern era (Appendix A).

The *Corpus Hippocraticum* recommends mandrake root as a sedative for "those who are troubled and ill" (*Loc. Hom.* 39; Potter, 1995, p. 78–79), to treat convulsions (*Loc. Hom.* VIII, 328.39; Potter, 1995, p. 79) and to treat tendons, applied as a warm poultice (*Loc. Hom.* 39: Potter, 1995, p. 78–79). The root was also recommended for inflammations of the rectum ("mandrake root, best fresh…you should wash thoroughly and cut, and then boil in diluted wine and apply as a plaster; the dry you grind and apply as a plaster in the same way") (*Fist.* 9; Potter, 1995, p. 404–405). In *De Morbo Sacro* (Morb II. 43; Aliotta et al., 2003, p. 212) Hippocrates mentioned the root to stop and calm quartan fevers.

The excerpt of the herbal 'Enquiry into plants' (*Historia plantarum*; Theophrastus, 1977) recommends mandrake leaves mixed with barley (*Hordeum vulgare* L.) as a poultice for treating wounds. The root, scraped and soaked in vinegar, is said to be useful for erysipelas and, also as a remedy for gout, to induce sleep and for love potions mixed with wine or vinegar (Amigues, 2006). In Dioscorides' *De Materia Medica* (IV 75; Beck, 2017, p. 279) mandrake fruits appear for the first time in a herbal book, mentioned as a soporific when eaten and smelled. Seeds are recommended for cleaning the uterus and to treat bloody vaginal discharge as a clyster. The leaves are above all recommended for dermatological ailments including abscesses, scrofulous swellings of glands, small tumours, indurations, abscesses caused by ulcers, as well as to treat eye inflammations, always applied externally. The root was recommended as a clyster (enema) for softening the belly, to expel the embryo, to induce menstruation and as a soporific. Taken orally, the root was recommended as an antidote in general, specifically for snake bites, as an emetic, aphrodisiac, a general painkiller for headache as well as for imminent amputations, as a soporific, to kill but also externally for treating erysipelas, scrofulous swelling of glands, tumours and joint pain. Besides the anaesthetising and sleep producing property of mandrake root, Ibn Sina (2012) mentions root powder mixed with vinegar "for an acute, fever producing disease characterized by diffusely spreading deep-red inflammation of the skin or mucous membranes and associated pustules" (p. 701) possibly corresponding to escalate. The root mixed with wheat or barley flour is recommended as a poultice for arthritis and elephantiasis (p. 701). The fresh leaves are said to remove freckles and reddish spots without causing irritation or burning when rubbed on the skin for one week. Modern reports from the Mediterranean area mention the root as an analgesic, soporific and sedative. From contemporary Turkey, Armenia, Iraq, Lebanon, Morocco and Spain, the use of the root as an aphrodisiac is reported as well as from 19th century England. From modern Turkey and North Africa, uses as an appetite inducing agent, for treating haemorrhoids, gynaecological problems as an (external) anti-inflammatory and antispasmodic are reported. Leaves are the preferred plant organ for treating skin problems such as chilblains in Spain, boils in Italy, wounds in Cyprus. Leaves are also considered antispasmodic in Northern Africa, carminative in Jordan, useful for gynaecological problems and good for respiratory conditions such as cough, asthma, and bronchitis in Jordan, Morocco and Northern

Africa where they were also reported to be applied externally for treating rheumatism. Moreover, leaves are used as sedatives in Jordan and as an anaesthetic in Israel and Morocco (Appendix A).

4.4 Phytochemistry of *Mandragora* sp.

The total alkaloid content of the roots of *M. autumnalis* was estimated to be between 0.2 and 0.3% (different samples, Bekkouche et al., 1993; Jackson and Berry, 1973). They are rich in tropane alkaloids such as scopolamine (hyoscine, in its racemic form 'atroscine') and L-hyoscyamine, which upon extraction provides the racemic mixture of L- and R-hyosciamine generally known as atropine (Dewick, 2002). Other tropane alkaloids from the roots are apoatropine, 3α-tigloyloxytropane, 3,6-ditigloyloxytropane, calystegines, α- and β-belladonnine. In addition, the pyrrolidine alkaloid cuscohygrine was obtained. Moreover, cumarins such as scopoletin (β-methylesculetin) and its glucoside scopoline were detected. Leaves were found to contain hyoscyamine, scopolamine, apoatropine, scopine and the cumarins herniarin, umbelliferone and angelicin while in seed extracts the presence of hyoscyamine, scopolamine, apoatropine, scopine, cuscohygrine and angelicin was determined. Analysis of the fruit pulp revealed the presence of scopoletin (β-methylesculetin) and volatiles (see below). From *M. officinarum* also isomeric N-oxides of (-)-hyoscyamine and isomeric N-oxides of (-)-hyoscine and norhyoscyamine were isolated (Phillipson and Handa, 1975) Calystegine (A3, B1, and B2) were found in both species but above all in the young leaves of *M. officinarum*. Table 2 lists the identified metabolites with their quantifications (when available) for species and organs. Main alkaloids and compounds found in *Mandragora* are represented in supplementary Table A.

The roots of flowering *M. autumnalis* (two samples analysed) from Morocco were found to contain 220 and 240 mg/100 g alkaloids of which 176 and 203 mg accounted for extracted atropine and 3 and 27 mg for scopolamine. With 60 and 90 mg/100 g the leaves were found to contain around one third of total alkaloid content with respect to the roots with 34 and 45 mg atropine and 1 and 24 mg scopolamine (Bekkouche et al., 1993). The roots of fruiting *M. autumnalis* were found to contain 120 and 180 mg/100 g total alkaloids with 104 and 108 mg atropine and 6 and 59 mg scopolamine. Leaves had a total alkaloid content of 30 and 60 mg/100 g with 20 and 47 mg atropine and 2 and 5 mg scopolamine. Seeds had 20 mg total alkaloids per 100 g with 6 and 10 mg atropine and 2 and 4 mg scopolamine (Bekkouche et al., 1993). There seems to be a quantitative and qualitative difference between the alkaloid and cumarin content of the different plant organs. Roots had an alkaloid/cumarin ratio of ca. 8:1 with scopoletin and scopoline as the major cumarins while leaves were found to have a ratio of 2.5:1 with herniarin, umbelliferone and scopoletin as the major cumarins (Al-Khalil and Alkofahi, 1996).

Up to 132 chemical components have been found in extracts of *Mandragora autumnalis* fruits (Hanuš et al., 2006). Main volatiles in *M. officinarum* berries were found to be ethyl butyrate (22%), hexanol (9%), and hexyl acetate (7%) sulfur compounds and γ-lactones (Fleisher and Fleisher 1994; 1994; Hanuš et al., 2005). Berries of *M. autumnalis* were found to contain ethyl esters of middle chain acids as major constituents as

well as ethyl caprylate, linoleic acid, n-hexyl acetate, ethyl caprate and ethyl caproate (Baser et al., 1998; Hanuš et al., 2005, 2006).

Table 2. Secondary metabolites of the different botanical drugs derived from *M. officinarum* and *M. autumnalis*. Concentrations are reported whenever provided. In case the organ is not specified concentrations refer to the whole plant. x= present; n.d. = no data; dm= dry mass; J.S.= juvenil stage; R.S.= reproductive stage; F.S.= fruiting stage. References: **1**. Jackson and Berry (1973), **2**. Jackson and Berry (1979); **3**. Carr and Reynolds (1912); **4**. Phillipson and Handa (1975); **5**. Dräger (2004); **6**. Bekkouche et al. (1994); **7**. Baser et al. (1998); **8**. Al-Khalil and Al Kofahi (1996); **9**. Fleisher and Fleisher (1994) (References **1-9** were reviewed by Hanus et al., 2005); **10**. Hanus et al. (2006); **11**. De Simone et al. (2008); **12**. Suleiman et al. (2010).

Recognized species (name in the original work)	**Organ**	**Hyoscyamine**	**Scopolamine (Hyoscine)**	**Atropine**	**Different alkaloids**	**Different secondary metabolites**
***M. autumnalis* (*M. autumnalis* and *M. vernalis*)**	Fresh roots	(1)	(1)		Cuscohygrine, apoatropine, 3α-tigloyloxytropan, 3,6-ditigloyloxytropane (1,2)	Scopoletin (β-methylesculetin), sitosterol and sugars (rhamnose, glucose, fructose, sucrose) (2)
***M. autumnalis* (*M autumnalis* and *M. vernalis*)**	Dried roots				Cuscohygrine, apoatropine, 3α-tigloyloxytropane, 3,6-ditigloyloxytropane, α-and β-belladonnine (1)	
M. autumnalis	Roots	(8)	0.02-0.03%; 24.6-28.6 mg/100 g (R.S.) (6) 0.05-0.006%; 23.2-31.4 mg/100 g (F.S.) (6) (8)	0.17-0.2%; 106.8-113.6 mg/100 g (R.S.) (6) 0,1%; 110.8-120.6 mg/100 g (F.S.) (6) (8)	Apoatropine, cuscohygrine, belladonnine (8,11) Calystegine A3 (30 µg/g dm) and B2 (20 µg/g dm) (5)	Scopoletin, scopoline, sucrose, chlorogenic acid (8)
M. autumnalis	Leaves		0.006-0.05% (F.S.) (6) 0.0005-0.002% (R.S.) (6) (8)	0.03-0.04% (R.S.) (6) 0.019-0.04% (F.S.) (6)	Apoatropine, scopine (8)	Herniarin, umbelliferone, angelicin (8)
M. autumnalis	Fruits					Scopoletin (β-methylesculetin) (2)
M. autumnalis	Unripe fruits			(8)	Scopine (8)	Herniarin, scopoletin, umbelliferone, angelicin (8)
M. autumnalis	Fresh ripe fruits					Volatiles: Ethyl caprylate (8.7%), linoleic acid (6.56%), n-Hexyl acetate (6.5%), ethyl caprate (6.15%), ethyl caproate (4.4%), ethyl laurate (3.19%), n-Hexyl butyrate (3.02%) among 100 constituents (7, 10).
M. autumnalis	Seeds		0.02-0.04% (6)	0.01-0.03% (6) (8)	Apoatropine, scopine, cuscohygrine (8)	Angelicin (8)
M. officinarum	Fresh roots	(1)	(1)		Cuscohygrine, apoatropine, 3α-tigloyloxytropan, 3,6-ditigloyloxytropane (2,11)	Scopoletin (β-methylesculetin), sitosterol, sugars (rhamnose, glucose, fructose, sucrose) (2)

M. officinarum	Dried roots		Cuscohygrine, apoatropine, 3a-tigloyloxytropane, 3,6-ditigloyloxytropane, α-and β-belladonnine (2,11)	
M. officinarum	Root		Calystegines A3 (48 µg/g dm), B1 (35 µg/g dm) and B2 (39 µg/g dm) (5)	
M. officinarum	Roots, stems (with leaves) and fruits		Isomeric N-oxides of (-)-hyoscyamine and isomeric N-oxides of (-)-hyoscine (4)	
M. officinarum	Leaves		Calystegine A3 (87 µg/g dm), B1 (44 µg/g dm) and B2 (80 µg/g dm) (5)	
M. officinarum	Young leaves		Calystegine A3 (200 µg/g dm), B1 (105 µg/g dm) and B2 (138 µg/g dm) (5)	
M. officinarum	Flower		Calystegine A3 (76 µg/g dm), B1 (40 µg/g dm) and B2 (69 µg/g dm) (5)	
M. officinarum	Fruits		Calystegine A3 (20 µg/g dm), B1 (17 µg/g dm) and B2 (30 µg/g dm) (5)	Scopoletin (β-methylesculetin) (2) Volatiles (ethyl butyrate (22%), hexanol (9%), hexyl acetate (7%) and sulfur containing compounds (> 7%) among 55 compounds) (9)
M. officinarum	Whole plant	(11)	3-senecioyloxytropane (11)	Whitanolides (mandragorolide A, mandragorolide B, larnaxolide A, whitanolide B, datura lactone 2, withanicandrin, salpichrolide C) (11, 12) Fatty compounds, coumarins (scopetlin scopolin), sterols (β-sitosteryl glucoside, β-sitosteryl glucoside-6-octadecanoate) (11)
M. officinarum (M. vernalis)	n.d.		Norhyoscyamine (pseudohyoscyamine) (3)	

4.5 Pharmacology of the main metabolites

Atropine and scopolamine are known as muscarinic antagonists with parasympatholytic properties. They prevent acetylcholine from exerting its muscarinic actions at postganglionic parasympathetic neuroeffector sites including smooth muscles, secretory glands and the CNS. The LD_{50} of atropine for an average human (ca. 80 kg) has been estimated to be around 453 mg (95% confidence interval 335–612 mg) (Goodman, 2010). Compared with the CNS effects of scopolamine, atropine is only 1/7th as potent (Goodman, 2010), while with respect to L-hyoscyamine, atropine is only around half as potent (Dewick, 2002, p. 298). Intoxications may cause chronic spasms, strong heartbeat, tachycardia, dilated pupils, amnesia,

hallucinations, inhibition of salivary secretion, perspiration, coma, and respiratory arrest (Dewick 2002; Goodman, 2010; Brayfield, 2017).

The therapeutic potential of calystegines seems to be based on the activity as selective glycosidase inhibitor, which could serve diabetic patients (De Simone et al., 2008). Calystegines were suspected to contribute to the toxicity of Convolvulaceae but this remains to be confirmed (Dräger, 2004).

4.6 Diachronic analysis of peak periods in use diversity and URs

In this section we trace the evolution of therapeutic uses and changes of the therapeutic consensus across time. According to the number of different medicinal uses in each historical period, the sequence is: Middle Ages (37), Renaissance (31), classical period (27), and modern era (21). The sequence of considered written sources per period is Renaissance (64), modern era (42), Middle Ages (39) and classical period (17) (Table 1, Fig. 1). Though the results are highly influenced by the accessibility and availability of literature sources we believe that this review reflects the written and cultural trajectory of mandrake. Uses of mandrake were more restricted in the classical period and reached highest versatility and popularity in the Middle Ages. Notwithstanding the higher number of textual sources during the Renaissance period, the versatility of recommended uses began to decline while medicinal uses are now again restricted to those regions where the plant grows naturally.

Most therapeutic use-records were collected for the Renaissance (235 URs from 64 sources; Table 1, Fig. 1), followed by the medieval (172 URs from 36 sources), classical (99 UR from 16 sources), and modern period (81 URs from 42 sources). The increase in the number of use-records from the Middle Ages to the Renaissance is conditioned by the diversification of textual sources triggered by the invention of the printing press. The relatively few use-records and the low versatility in the modern era shows the abandonment of mandrake as a source of botanical drugs (but see also section 4.9).

While for most ICPC groups treatments with mandrake derived drugs appear in all time periods, each period is characterized by one or two relatively dominant use groups (Fig. 2). The figure shows the relative prevalence of groups A (general and unspecified), S (skin) and N (neurological). Group A retains, more or less, the same importance across all time periods. The relative importance of group N is highest in the Middle Ages and that of group S in the Renaissance. The most dramatic decline in number of use-records occurred for the ICPC use group S between the Renaissance period and the modern era.

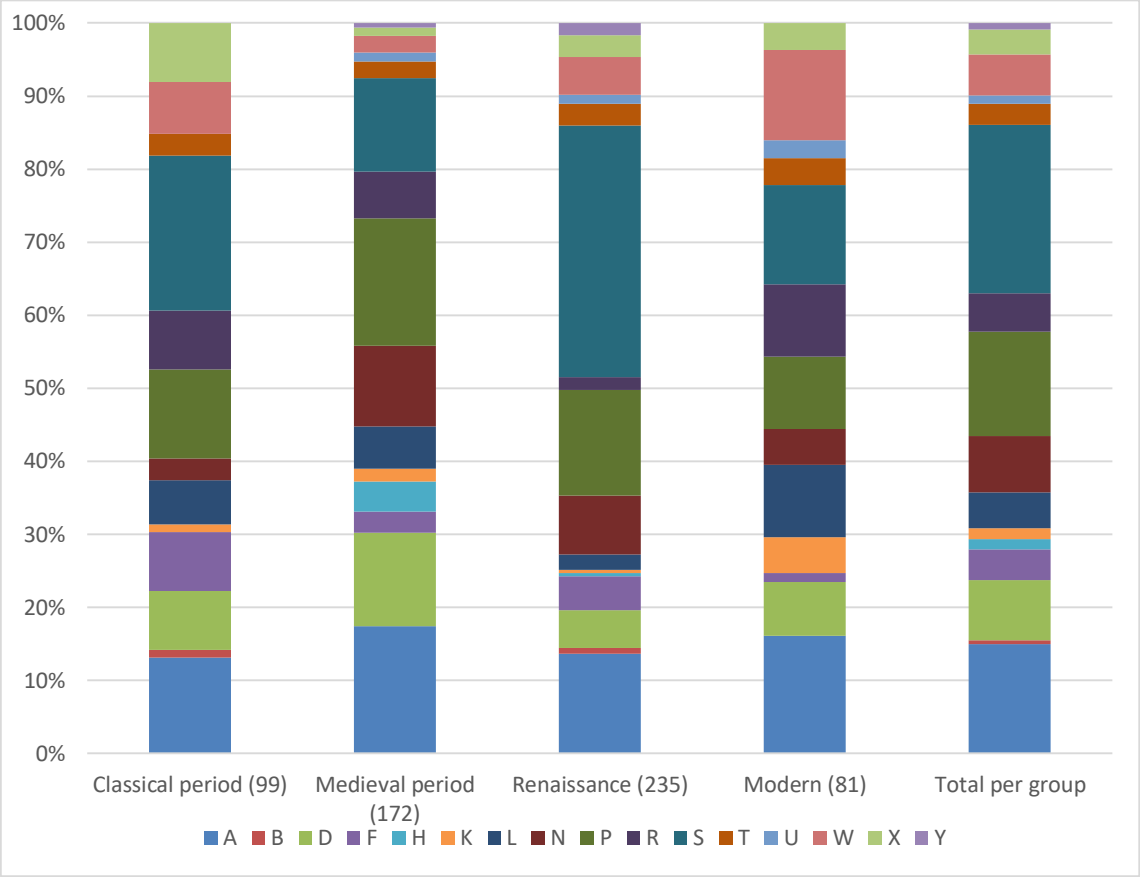

Figure 2. The relative distribution of the pathological groups treated with mandrake over time. The proportions of pathological groups treated in each period are presented, and the total number of uses per period is given in parenthesis. For actual numbers in each category, see Table 1.

The relative prevalence of the four most cited groups (S, A, N and D) varies from 70% in the Renaissance to 50% in the modern era (Fig. 2). The relative proportion of some categories (e.g., K, W) have increased in the last two centuries. The use for ICPC group W including aphrodisiacs and amatory attraction persists to the modern era, which appears like a folkloristic relict from biblical times. Although uses in group S are external (mostly with leaves), thus without the risk of tropane-alkaloid intoxications, uses increased in the Renaissance but declined in the modern era. The reduction of the relative prevalence of remedies in ICPC groups A and N could be explained with the development of synthetic anaesthetics (A) and drugs for sleep disturbances or depression (N) (see Fig. 3 and supplementary Table A).

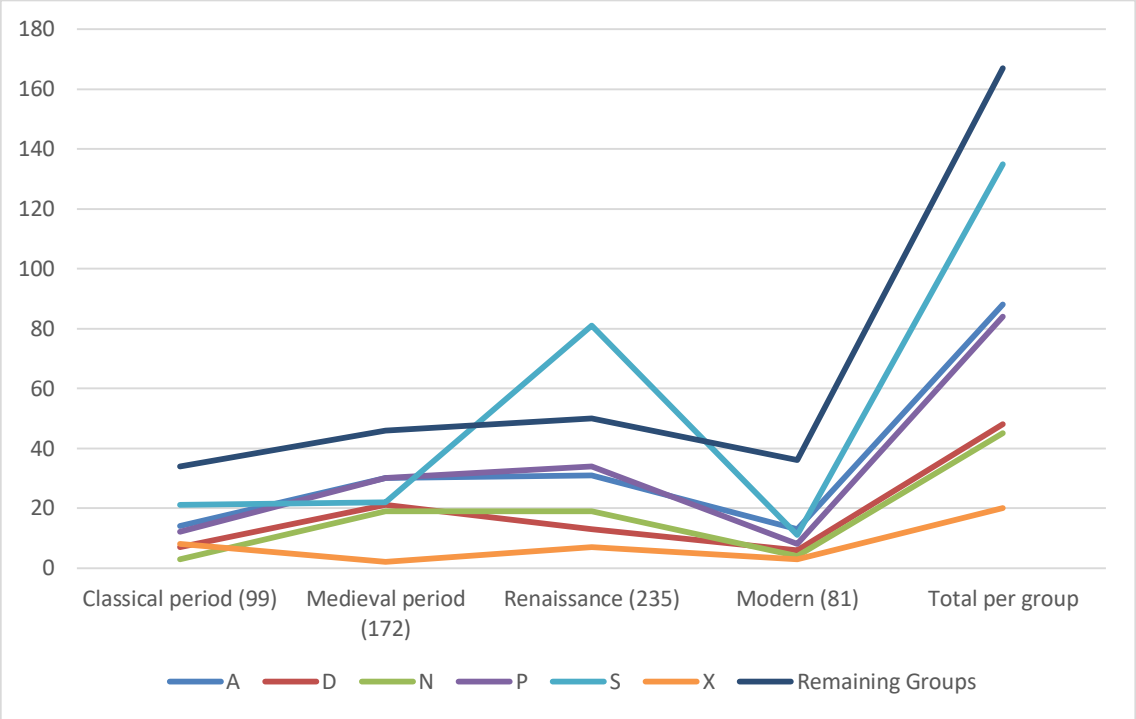

Figure 3. Distribution of medicinal uses of the mandrake through history in selected pathological groups (PGs), according to the number of use records.

Of the 39 conditions for which mandrake derived drugs have been used, 17 (43%), in addition to its frequent mention as an intoxicant, are reported across all four time periods. This seems to be a considerable share that is likely influenced by effectiveness (see section 4.8). However, due to a lack of studies adopting a similar approach and perspective it is difficult to the tell whether the amount of conservation is above or below average. Nine conditions have been recorded in three time periods, eight have been recorded in two periods (four of them in the Middle Ages and Renaissance) and five were cited just in one period, four of them only in the medieval (supplementary Table B).

4.7 Analysis of uses in native and non-native territories

Here we compare the medicinal uses in areas where the plant is considered native *vs.* non-native areas in to order to detect possible differences associated with cultural particularities and new therapeutic applications.

Mandrake is a Mediterranean species (see Volis et al., 2015 for a distribution map of the complex *M. officinarum* - *M. autumnalis*) and was introduced to middle and northern Europe relatively late. The plant was introduced to England in the 12th and to Germany in the 16th century (Van Arsdall et al., 2009; Simoons, 1998). Its cultivation from seeds is not difficult, and cultivation success has permitted experimentations with mandrake derived drugs in areas where mandrake is not native.

Table 1 shows the number of URs from native and non-native territories while Fig. 4 is showing the proportions, for IPCP-2 use groups. Most of the least frequently mentioned conditions (below three URs) stem from non-native territories (all periods and conditions) including nosebleed, rabies, paralysis and bone

fracture indicating that the drug was experimented with for applications that stood not the test of time. Exceptions are the uses for tooth problems, for which we found one reference in native and one in non-native territory, and jaundice, with a single citation from medieval Italy (Appendix A). Among the 12 most cited conditions (above 10 URs), percentages for citations in native territories vary from 42% for headache (N), to 92% for feeling anxious/use as a sedative (P). In total, 62% of the URs (in Table 1) stem from native territories. Fig. 4 shows that ICPC groups K, D, R and W are those with the highest share of native uses.

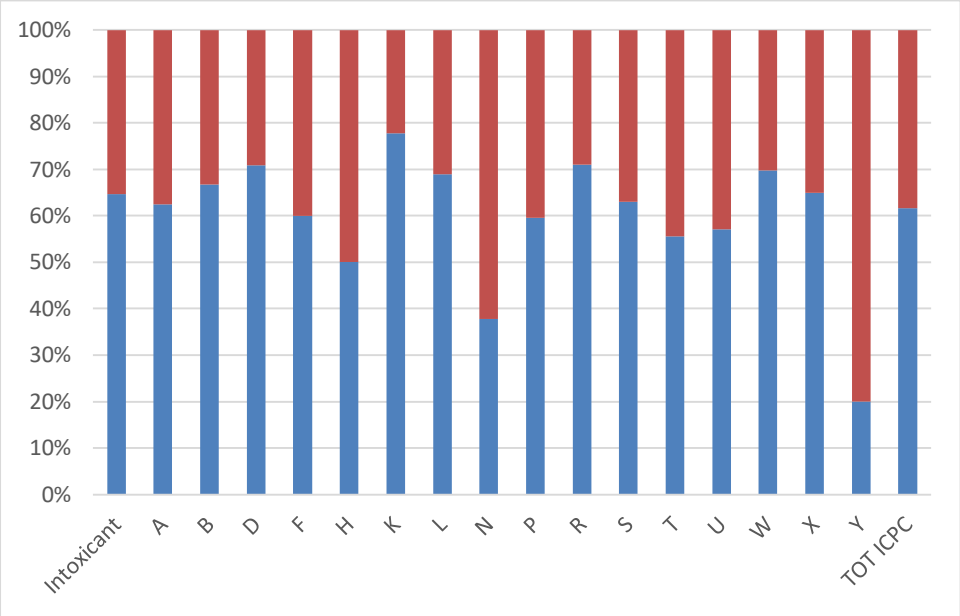

Figure 4. Proportion of UR from territories where the plant is native (blue) or non-native (red) across ICPC groups.

4.8 Pharmacology related to traditional uses

Here we discuss and try to explain the traditional uses in light of phytochemical and pharmacological literature data for those 14 conditions for which such a discussion is meaningful. For another 25 conditions we found no convincing explanation other than the drug's general amnesic effect.

4.8.1 Aphrodisiac (W, four time periods)

The allegedly aphrodisiac property of mandrake was first mentioned in the Old Testament and known in Greece, Rome and Iran throughout all time periods (Table 1, Appendix A). Mandrake was historically associated with both, Aphrodite (Greek love Goddess) and Circe (Rahner, 1971; Lee, 2006). During the Renaissance period mandrake became a love symbol also in Europe (Bosse-Griffiths, 2001). In contrast to the Old Testament, in *De Materia Medica,* and subsequently in other texts, not the fruits but the roots were described as having aphrodisiac properties. Though, still today, fruits of mandrake are collected in Israel by Orthodox Jews and Arabs and are given to "overcome bareness" (Patai, 1944; Dafni and Khatib, 2017) and the plant is still acknowledged for this purpose in Spain, Turkey, Armenia, Iraq, Lebanon and Morocco (Appendix A).

Besides being mentioned in Genesis, mandrakes and their fruits are also mentioned in the Song of Songs 7:13 “The mandrakes give forth fragrance …” and in the Testaments of the Twelve Patriarchs; Testament of Issachar 1:3, 5, 7: “My brother Reuben brought mandrakes from the field ... and there were fragrant apples growing above the water beds in the land of Aram” (Fleisher and Fleisher, 1994). The quality that is highlighted in those texts, as noted by Fleisher and Fleisher (1994), is the fragrance of the fruits. A fragrance that these authors describe as being savage, intense and unique, composed of esters and sulfur-containing compounds, which gives it a fruity but raunchy scent. Another fruit with ascribed aphrodisiac properties containing sulfur compounds is durian (*Durio* spp., Malvaceae) (Brown, 1997). Fruit volatiles are thought to have evolved in the context of fruit dispersal and to be important cues for health and nutritional values (Goff and Klee, 2006). Such volatiles interact in a combinatorial way with an array of the 390 existing odorant G protein-coupled receptors expressed in the olfactory epithelium (Malnic et al., 1999; Goff and Klee, 2006; Olender et al., 2008). These olfactory receptors are not confined to the nose epithelium but are found in a variety of tissues and cells throughout the body and thought to be important drug targets, though their potential has only yet started to be explored (Drew, 2022).

Being devoid of mind-altering alkaloids, the aphrodisiac quality of mandrake fruit-flesh seems to be associated with its provocative scent. It is, however, not clear whether the intoxicating seeds were discarded or whether the whole fruits were used as an aphrodisiac in biblical times. The narcotic effects of the alkaloid bearing roots recommended as an aphrodisiac (e.g. Dioscorides) would have an impact on self-control and facilitate abuse, as reported for other Solanaceae (Benítez et al., 2018).

4.8.2 Analgesic and anaesthetic uses (A, four time periods)

Mandrake root was one of the most important drugs used for analgesic and anaesthetic purposes (e.g., Fleisher and Fleisher, 1994; Chidiac et al., 2012; Everett and Gabra, 2014). The first authors describing uses as an anodyne were Demosthenes in the 3rd century BCE (Deforêt, 1993) followed by Rufus of Ephesos (1st century CE; Keyser and Irby-Massie, 2008) and Dioscorides (*De Materia Medica* IV, 75.7; Beck, 2017). Analgesic and anaesthetic properties were widely mentioned in the Middle Ages and Renaissance period and still reported in ethnomedical field studies from the Middle East and Northern Africa (Appendix A). In the Middle Ages an anaesthetic preparation called “*spongia somnifera*” was much in use. Juices of mandrake, henbane (*Hyoscyamus* spp.), opium (*Papaver somniferum* L.), hemlock (*Conium maculatum* L.), ivy (*Hedera helix* L.) and other plant drugs were mixed and made to be absorbed by a sea sponge that was then dried-out in the sun. Before its use, the sponge was soaked in water and put to the nostrils of patients prior to surgical interventions (Keys, 1996; Prioreschi, 2003). From the literature it does, however, not become clear whether the juice was also poured into the nostrils, which would have made the alkaloids bioavailable, possibly via their absorption across the mucous membranes. Another question resulting from such concoctions is whether the ivy bidesmosides may increase the absorption of the alkaloids.

In a continuation of the tradition of mixing Solanaceae alkaloids with opioids, scopolamine was administered in combination with morphine to induce the so-called "twilight sleep" for relieving obstetric pain for the first time in 1902 (Keys, 1996). This practice remained controversial and depended on exact timing and dosing of a stable scopolamine solution under continuous clinical surveillance (NYT, 1915; Leavitt, 1980). Women choosing to give birth under the effect of scopolamine and morphine lost control over their body while their memory got obliterated. Moreover, the new-borns were occasionally found to be somnolent and affected by oligopnoea (NYT, 1915; Leavitt 1980). The amnesic effect of scopolamine made women not only forget the pain but also the fact that they had given birth. An English physician is cited in the article published in the NYT in 1915 as follows: "if there is no memory of pain, it is equivalent of having had no pain". Inducing such a semi-conscious state for easing childbirth was gradually abandoned but scopolamine was used for shortening labour until the 1960's (Leavitt, 1980). Scopolamine butylbromide (20 mg) given intravenously shortens labour without any adverse effects on mother and new-born (Sekhavat et al., 2012) which seems to be associated with traditional uses of mandrake as an abortive.

However, atropine and scopolamine cannot be considered analgesic drugs (Chidiac et al., 2012). Swallowing when moderately intoxicated with Solanaceae alkaloids is in fact very painful (cf. Goodman, 2010). Only in combination with analgesic compounds anaesthesia may be obtained and potentiated by anticholinergics (Chidiac et al., 2012). Blocking muscarinic and nicotinic receptors prevents the antinociceptive effect of acetylcholine which stands in contrast with the use of atropine and scopolamine containing drugs for inducing analgesia (Bartolini et al., 2011). However, at low doses (1-100 µg/kg) atropine was shown to induce analgesia in mice and rats while at higher doses (5 mg/kg) hyperalgesia was obtained (Ghelardini et al., 1990). *In vitro* studies showed that at very low concentrations (10^{-14}-10^{-12} M) atropine has an indirect cholinomimetic activity by antagonizing muscarinic presynaptic auto-receptors (Ghelardini et al., 1990; Bartolini et al., 2011). However, this activity was only confirmed for the dextro-isomer and not for the native laevo-isomer (Bartolini et al., 2011). Low atropine doses might be achieved with some specific administrations such as for treating toothache (where the root was applied to the aching tooth). However, for the inherent laevo-isomer no analgesic effects are reported and it is not clear how easily the laevo-isomer of hyoscyamine racemises into atropine with traditional drug preparation methods including the preparation of the 'somniferous sponges'. Be that as it may, for achieving analgesic effects mandrake and its constituents as well as other Solanaceous drugs seem not to be a reliable source.

4.8.3 Skin disorders (S, four time periods)

Considering the early records recommending mandrake leaves for skin disorders and the importance of textual information in the transmission of knowledge (Leonti and Verpoorte, 2017) the continuous use in dermatology is not very surprising (specifically, inflammations, skin problems and animal bites). It stands, however, in contrast with today's widespread popular knowledge of mandrake's narcotic properties. From the leaves, two simple coumarins (herniarin and umbelliferone) as well as a furocoumarin (angelicin) have been isolated. Furocoumarins are known to be photosensitizing and phototoxic agents inducing skin

pigmentation. However, they can also induce dermatitis. Linear as well as angular furocoumarins have been used in photochemotherapy to treat vitiligo, psoriasis, atopic dermatitis and *Mycosis fungoides*. Such cumarins have also genotoxic, mutagenic and carcinogenic properties which precludes prolonged applications (Falbe and Regitz, 1997). *In vitro* studies focusing on the antimicrobial properties of *Mandragora* sp. extracts reported only moderate activity (Obeidat, 2011; Obeidat et al., 2012; Jodallah, 2013). However, the antimicrobial potential of a direct application of fresh plant material on the skin as applied in traditional medicine is generally poorly investigated (Mazzei et al., 2020).

4.8.4 Digestive symptoms (D, four time periods)

Scopolamine has antispasmodic effects on smooth muscles, which explains why mandrake has been used since Greek antiquity for treating colic pain and spams of the gastrointestinal tract. Scopolamine has also been used as an adjunct in peptic ulcer disease (Brayfield, 2009) and might explain the recommendation of mandrake for gastrointestinal ulcers from the Near East in the 12th century.

4.8.5 Psychological symptoms / Depression (P, four time periods)

Scopolamine given i.v. (4 µg/kg) alleviates depression in patients with major depressive disorders or bipolar disorders (Brayfield, 2009) and might be at the basis for the historic recommendations to treat suicidal mania and melancholy with mandrake drugs.

4.8.6 Epilepsy (N, two time periods)

The recommendations of using mandrake for epilepsy might be related to the modern application of atropine in case of anoxic seizure common in children and triggered by cardiac syncope (Brayfield, 2009).

4.8.7 Irregular heartbeat (K, two time periods)

The recommendations of using mandrake for heart disease and blood circulation barely mentioned in the literature from the Middle Ages and Renaissance can be explained with the effects of atropine on the heart rate. Atropine is still used in the treatment of bradycardia and the absence of ventricular contractions (asystole) of various causes (Brayfield, 2009).

4.8.8 Respiratory symptoms (R, four time periods)

Anticholinergic agents are potent bronchodilators (Gross et al., 1984; Brayfield, 2009), which explains the recommendation of mandrake for treating respiratory problems from the 1st century to modern era. Combined with antihistamines, atropine has also been used for the symptomatic treatment of common cold (Brayfield, 2009), an indication for which mandrake is reported since Greek antiquity.

4.8.9 Eye symptoms (F, four time periods)

Uveitis, iritis and strabismus can be treated with a solution of atropine (Brayfield, 2009) corresponding with the historic use of a mandrake unguent applied for eye problems.

4.8.10 Urinary symptoms (U, three time periods)

Antimuscarinics have been used to control urge incontinence (Brayfield, 2009) and atropine has been found to lower the incidence of catheter-related bladder discomfort in patients with urethral catheterization (Şahiner et al., 2020) but it is not clear how these properties relate to the recommendations of using mandrake for urinary stones and painful urination.

4.8.11 Poisoning / Antidote (A, three time periods)

The few use records recommending mandrake as an antidote might be related to muscarine intoxications with mushrooms or poisons made from *Galanthus* spp. ('moly') containing the acetylcholine-esterase inhibitor galanthamine (Brayfield, 2009; Plaitakis and Duvoisin, 1983; Lee, 1999, 2007).

4.9 Myths as a cue for the rise and fall of mandrake in medicine

A lot has been written about mandrake and the myths and legends surrounding the plant (e.g., Randolph, 1905; Thompson, 1934; Carter, 2003; Van Arsdall et al., 2009). Some of them are even reflected in the local vernacular names the plant assumes in the different languages spoken in its natural range (see Dafni et al., 2021). We briefly comment here on those that are more widespread or are related to the therapeutic use of the plant.

Theophrastus (1977, p. 255-161) reported that, in general, the collection of medicinal plants and especially of roots was guided by myths and superstitions. The narratives foresee punishments for root-diggers, including the swelling of one's body, loss of eyesight and the contraction of *prolapsus ani* for those who disregard the rules imposed. Specifically, Theophrastus reported for mandrake "It is said that one should draw three circles around mandrake with a sword, and cut it with one's face towards the west; and at the cutting of the second piece, one should dance round the plant and say as many things as possible about the mysteries of love" (Theophrastus, 1977, p. 259). Similar legends were told for the collection procedure of other plant roots showing that these legends were not specifically restricted to mandrake (Randolph, 1905).

It is probably Matthioli (1568, IV:78) who should get the point for having first answered the question about the purpose of the legends surrounding the harvesting of mandrake roots. The planting of the rumour about the danger mandrake root harvesting entails as well as the rituals and procedure recommended to be adopted helped the cause of the professional root-diggers ('*rhizotomoi'*) in keeping undesired competitors away from the business. At the same time such legends added to the root's commercial value and were effective in transmitting the fame of mandrake to the extent that the plant is now known worldwide (see also Randolph, 1905). These legends transport medical knowledge and are memes.

Mandrake was described by several authors as a panacea (e.g., Wright, 1845; Laza Palacios, 1953; Gottlieb, 1962; Schultes, 1976; Guerrino, 1969; Carter, 2003; Bennett, 2007). However, from the therapeutic point of view our data do not support this idea. A panacea is "a remedy for all ills and difficulties", and while mandrake has been recorded for 16 of the 17 ICPC chapters and 39 conditions (out of the 685 total ICPC

conditions) across the ages, at no point in history was it recommended for 16 ICPC chapters altogether. The superstitious beliefs associated with its anthropomorphic shape and the memory obliterating effect have probably contributed to the idea that mandrake was a panacea.

Moreover, the imaginary associations that mandrake offers may be manifold. Several of them are reflected in the vernacular names of the plant in the different languages spoken in its distribution area. While the often-forked taproot has an anthropomorphic character, dried fruits look like a scrotum (several vernacular names reflect this association; see Dafni et al., 2021) or a purse filled with coins (hence its myth and use for increasing fortune in Germany, reflected in names such as *geldmännchen* ["money manikin"] or *glücksmännchen* ["good luck manikin"]; see De Cleene and Lejeune, 2003, and Dafni et al., 2021). The imaginary power of mandrake which made the plant attractive to charlatans and magical practices is surely increased by its pharmacologic properties and *vice versa*. This folkloristic popularity and associated superstition is thought to have been one of the reasons why medical doctors turned away from using mandrake towards the end of the Middle Ages (Fleisher and Fleisher, 1994). Medical doctors were also aware of the unreliable narcotic properties when used as an anaesthetic in surgery and as an analgesic (Renou, 1657, p. 345; Woodville, 1832). The second reasons for the decline of mandrake as an analgesic and anaesthetic is certainly associated with the rise of organic and inorganic chemistry and the production of potent anaesthetics and analgesics with more reliable properties and fewer side effects. However, the volatile anaesthetics ether and chloroform introduced after 1846 were not without side-effects. Increased salivation was common while unexplainable cases of cardiac arrest were observed for ca. 1 in 3,000 patients treated with chloroform and in 1: 14,000 treated with ether (Holzman, 1998). Premedication with atropine was later introduced to prevent cardiac arrest mediated by the *vagus* nerve as well as from increased salivation (Holzman, 1998; Brayfield, 2009). This is how after thousands of years of use as a soporific, anaesthetic and anodyne applied through botanical drugs and concoctions, atropine found its place in modern anaesthetic medicine as a prophylactic medication and antidote for the new anaesthetics (Holzman, 1998).

5. Conclusions

Mandrake has been in continuous therapeutic use since the dawn of written history and is one of the plants with the oldest written record. Some of the mandrake's medical applications have remained in continuous use especially in the Near East and the Arabic World, such as that as an aphrodisiac and analgesic, or the use for spasms of the gastrointestinal tract. Recommended uses limited to certain periods of time likely reflect experimental approaches and idiosyncratic knowledge. The fact, that from the *Corpus Hippocraticum* no uses of the mandrake fruits are passed down, and that neither Dioscorides nor Galen mentioned mandrake fruits as an aphrodisiac, fosters the idea, that this knowledge and use was confined to Semitic language speaking peoples, who, in fact, keep this custom alive.

The legends surrounding mandrake together with its morphology, scent and narcotic effects propelled its fame also in European medicine. However, the extent to which magical and superstitious believes about mandrake spread among the population in the Middle Ages might have begun to deter medical doctors from applying mandrake in the pursuit to preserve their medical reputation. The trajectory of mandrake in *materia medica* reflects in many facets the development of medicine in Europe. On the other hand, the trajectory of memes associated with mandrake start with the love apples and end with a crying mandrake telegram icon. Several therapeutic uses can be explained with the pharmacology of its metabolites, though today either safer and more reliable products, or the purified alkaloids atropine and scopolamine and their semisynthetic derivatives have eclipsed mandrake as a drug. While the pharmacology of the main constituents is well elucidated, the taxonomic dispute about the genus *Mandragora* in Europe continues for 2000 years.

Authors' contribution

AD and GB designed the study and performed most of the literature search and analysis. BB performed the ancient literature analysis. GB and ML wrote the article. SV with the medical analysis of the data. All authors approved the MS. The authors declare that they have no conflict of interest.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2022.115874 .

Appendix A

Medical uses of mandrake in various historical periods (selected references). Uses sorted chronologically in columns. Conditions/symptoms ordered in groups following the ICPC–2 classification (ICPC–2 category name in italics, code after condition name). We have omitted the word "century" after the number and added BCE or CE as necessary only in the column "classical period". For sources in classical and modern periods mentioning the plant organ: FR = fruit; LF = leaf; PL = plant; RT = root.

Category / Medicinal use	Classical period: Greece and Rome	Medieval (5th century–1492)	Renaissance period (1492-1899)	Modern (1900 onwards)
Toxic effects				
Narcotic / Hallucinogenic	**Ancient Greece**: *4th–3rd BCE*: Theophrastus, *Enquiry into Plants* IX, 9.1 (Amigues, 2006:24); *1st CE*; Iulius Bassus (Keyser and Irby-Massie, 2008:45) (Narcotic). **Ancient Rome**: *1st BCE–1st CE*: Antikhos Paccius (Keyser and Irby-Massie, 2008:95) (Narcotic); *1st CE*: Celsus III, 18.12 (Spencer, 1935:297); Celsus V, 25.2 (Spencer, 1935:61); Dioscorides IV,75,3 (Beck, 2017:279) (to kill, RT); Pliny, 25, 150 (König, 1996:102–105, cf. Bonet, 2014:418) (Narcotic).	**Spain**: *7th*: Isidore of Seville (Barney et al., 2006:351) (Sedative); *12th*: Al-Isbili, 2007 II:449 (Lethargy); *12th–13th*: Ibn al-Baytar (Leclerc, 1883:419) (Stupefying); *14th*: Ibn al-Jatib (Vázquez de Benito, 1998:767–769) (Narcotic). **Italy**: *9th–12th*: Goehl, 2015:312 (Narcotic). **Byzantine Empire**: *4th*: Pseudo-Apuleius Herbarium 131 (Randolph, 1905:511) (Narcotic); *7th*: Paul of Aegina, V, 49 (Adams, 1861:218) (Narcotic). **Syria / Iraq**: *12th*: Budge, 1913 II:257 (Narcosis).	**England**: *17th–19th*: Dale, 1693: 269; James, 1747:365; Alston, 1770:479; Strother, 1729:64; Redwood, 1857:416 (Narcotic). **Sweden**: *18th*: Linnaeus, 1782:72 (Narcotic). **Germany**: *17th*: Schröder, 1685:622; Geiger, 1839:568 (Narcotic). **Belgium**: *19th*: Nysten, 1840:522 (Narcotic). **France**: *17th–19th*: Pomet, 1694:135; Alexandere, 1759:286; Bouillet, 1874:1024 (Narcotic). **Spain**: *16th*: Laguna, 1555:423 (To kill); *18th*: Gómez Ortega, 1784a:401 (Narcotic, somnolent). **Italy**: *16th*: Matthioli, 1568: IV:78 (Staub et al., 2016) (Antidote, to kill). *18th–19th*: Étienne-François, 1756:432; Tessari, 1762:177; Zucchi and Ranzoli, 1854:516 (Narcotic).	**Spain**: Carrió, 2003:479; Dávila et al., 2008:348 (Hallucinogenic). **Jordan**: Aburjai et al., 2007:298 (Narcotic, LF). **North Africa**: Boulos, 1983:167 (Narcotic, RT). **Morocco**: El-Hilaly et al., 2003:156; Bnouham et al., 2006:26 (Narcotic; FR, LF).
Pathological group (ICPC–2 acronym)				
Pain relief / Analgesic / Anodyne (A01)	**Ancient Greece**: *1st BCE–1st CE*: Silo (Keyser and Irby-Massie, 2008:741) (Analgesic intestinal remedy). **Ancient Rome**: *1st CE*: Dioscorides, IV, 75.4 (Beck, 2017:279) (Pain; RT); Pliny, 25,150 (Bonet, 2014:418); *1st CE*: Celsus V, 25.3 (Spencer, 1935:295) (Toothache); *2nd CE*: Galen (Adams, 1849:288) (Pain).	**England**: *11th*: Van Arsdall, 2012:133; *12th*: Black, 2012:133 (Pain relief). **Spain**: *7th*: Isidore of Seville **(**Barney et al., 2006:351) (Pain); *14th*: Armengaud Blaise No. 64 (Mcvaugh and Ferre, 2000:149) (Sedation of pains). **Byzantine Empire**: *4th–15th*: Ramoutsaki et al., 2002b:554 (Pain). **Iran**: *10th–11th*: Ibn Sina (Zargaran et al., 2016:474) (Hot migraine, analgesic).	**Sweden**: *18th*: Linnæus, 1782:72 (Anodyne). **England**: *17th*: Culpeper, 1794:264 (Toothache); *18th–19th*: James, 1747:365; Quincy, 1782:489; Culpeper in Scarborough, 2010:XIV,87; 1794:264; Woodville, 1832:236 (Pain); Hill, 1751:405; Alston, 1770 I:479; Redwood, 1857:416 (Anodyne; LF). **Germany**: *18th*: Weinmann, 1742:349 (Anodyne). **France**: *18th–19th*: Geoffroy, 1743:4; Martin-Lauzer, 1856:462 (Pain). **Spain**: *16th*: Laguna, 1555:423 (Pain); Riddell, 1925:55 (Toothache).	**Turkey**: Aydin et al., 2006:169; Mert et al., 2008:833; Fakir et al., 2009:39; Fakir et al., 2016:321 (Pain relief, RT); Ozturk et al., 2011:202 (Analgesic; RT). **Iran**: Gorji, 2003:332 (Analgesic). **Jordan**: Aburjai et al., 2007:298 (Throat pain; LF). **Israel and Palestine**:

		Syria / Iraq: *12th*: Budge, 1913 II:503 (Pain), Ibid., 334 (Toothache). **Iraq**: *11th*: Ibn at-Tilmīd (Kahl, 2007:186) (Toothache). **Egypt**: *12th*: Maimonides (Muntner and ben Maimon, 1942:154) (Analgesic).	**Italy**: *16th*: Matthioli, 1568: IV:78 (Staub et al., 2016) (To suppress pain; to mitigate pain); *18th*: Étienne-François, 1756:432 (Pain).	Jaradat, 2005:12 (Pain after operation; PL). **North Africa**: Boulos, 1983:167 (Pain sedation, throat pain, RT); Anonymous, 2005:154 (Analgesic; RT, LF).
Anaesthetics (A01)*	**Ancient Greece**: *3rd BCE*: Demosthenes (Deforêt, 1993:44) (Somniferous); *1st CE*: Rufus of Ephesos (Keyser and Irby-Massie, 2008:721) (Anaesthetic). **Ancient Rome**: *1st CE*: Dioscorides, IV, 75, 7 (Beck, 2017:280) (Anaesthetic; RT); Pliny, 25, 150 (König, 1996:102–105) (Anaesthetic; RT, LF); Wynbrandt, 2000:100 (Soporific used during dental procedures).	**Spain**: *7th*: Isidore of Seville (Etymologies XVII, 9.30; Barney et al., 2006:351); Giuffra, 2013:36; Sharpe, 1964:35 (Sedation in surgery). **Italy**: *11th–13th*: Antidotarium Nicolai (Everett and Gabra, 2014: passim) (Component of the "Great rest" anaesthesia). **Southern Europe**: *Before 6th CE*: Pseudo-Dioscorides (ex herbis feminis 15; Giuffra, 2013:36) (Anaesthetic). **Byzantine Empire**: *4th*: Pseudo-Apuleius Herbarium 131 (Giuffra, 2013:36) (Anaesthetic). **Iran**: *10th–11th*:; Ibn Sina, 2012; Gruner, 1930:413 (Anaesthetic; RT).	**England**: *16th–18th*: Gerard, 1597:282 (Mitigate pain); Mitchell, 1959:194 (Anaesthetic). **France**: *16th*: Abroise Rare (Juvin and Desmonts, 2000:267) (Component of "Spongia somnifera"). **Spain**: *16th–18th*: Laguna, 1555:423 (Painkiller for amputations; sedation for surgery); Robredo, 1646:4; Geoffroy, 1743:4 (Somniferous). **Italy**: *16th–19th*: Matthioli, 1568: IV:78 (Staub et al., 2016) (Painkiller for amputations, pain-to suppress-to mitigate); Zucchi and Ranzoli, 1854:516 (Anaesthetic in surgery). **Serbia**: *15–16th*: Jarić et al., 2011:77 (Anaesthetic). **Turkey**: *Anatolia*: *15th*: Ganidagli et al., 2004:167 (Anaesthetic).	**Iran**: Ainslie, 1826 I:207 (Anaesthetic). **Israel and Palestine**: Jaradat, 2005:12 (Anaesthetic; PL). **Morocco**: Bnouham et al., 2006:26 (Anaesthetic; RT, LF).
Fever / Antipyretic (A03)	**Ancient Greece**: *5th –4th BCE*: Hippocrates, Morb II. 43 (Aliotta et al., 2003:212) (Stops and/or reduces quartan fever; FR).	**England**: *12th*: González Blanco, 2018:116 (All kind of fevers). **Spain**: *14th*: Armengaud Blaise No.64 (Mcvaugh and Ferre, 2000:149) (Fever). **Italy**: *12th*: Platerius (Goehl, 2015:311–312) (Fever).	**England**: *18th*: Strother, 1729:64 (Fever). **France**: *18th*: Geoffroy, 1743:4 (Fever). **Serbia**: *15th–16th*: Jarić et al., 2014:1366 (Antipyretic).	

		Byzantine Empire: *4th–15th*: Ramoutsaki et al., 2002b:554 (Fever). **Syria / Iraq**: *12th*: Budge, 1913 II: 334, 483 (Intermittent fever). **Iraq**: *10th–11th*: Ibn Sina, 2012 (fever; RT); *11th*: Ibn at-Tilmīd (Kahl, 2007:186) (Fever).		
Poisoning / Antidote / Poisoning / Intoxication (A84-A86)	**Ancient Greece**: *1st BCE–1st CE* (?): Epainetēs (Keyser and Irby-Massie, 2008:285) (For intoxications); Arninas of Indos (Keyser and Irby-Massie, 2008:124) (Antidote).	**Iraq**: *10th*: Ibn Wahshiya (Levey, 1966a:12, 56, 92, 94) (To treat poisonings); *10–11th*: Ibn Sina, 2012 (Poison antidote; LF). **Egypt**: *Cairo Geniza*: *11th–13th*: Lev, 2007:287 (Poisoning).		
Infectious diseases: Rabies / Elephantiasis (A78) / Viral disease (A77)		**England**: *12th*: Black, 2012:133 (Rabies). **Iraq**: *10th*-*11th*: Ibn Sina, 2012 (elephantiasis, scarlet fever; RT).		
Spleen disease (B99)	**Ancient Rome** *1st CE*: Celsus V, 25, 3 (Spencer, 1935:60) (Spleen).		**France**: *18th*: Geoffroy, 1743:4 (Hard tumors of the spleen) **Italy**: *18th*: Étienne-François, 1756:433 (Spleen tumor).	
Digestive symptoms (D29) / *Stomach disorder* (D87) / *Constipation*, Purgative, Cathartic (D12) / Gas (D08) / *Vomiting*, Emetic (D10) / *Diarrhoea* (D11)	**Ancient Greece**: *1st BCE–1st CE*; Euskhēmos the Enunch (Keyser and Irby-Massie, 2008:323) (Colon remedy); *1st CE*: Nikostratos (Keyser and Irby-Massie, 2008:582) (Colic remedy); Nikostartos (Keyser and Irby-Massie, 2008:582) (Colic, stomach remedy). **Ancient Rome**: *1st CE*: Dioscorides IV 75, 3 (Beck, 2017:279) (Brings up phlegm and bile, emetic; RT); Celsus V, 25.3 (Spencer, 1935:60) (Intestinal gripping, cramps).	**Germany**: *8th*: Lorsch pharmacopoeia (Stol, 1992:354–355) (Digestive problems). **Byzantine Empire**: *6th–7th*: Thomson, 1955 (in Scarborough, 2010:XIV, 87) (Diarrhoea). **Syria–Iraq**: *12th*: Budge, 1913 II:494 (Diarrhoea, constipation); Ibid. 334, 408 (Stomach pains); Ibid. 483 (Gastrointestinal problems); Ibid. 486 (Diarrhoea); Ibid. 334 (Flatulence); Ibid. 334, 408 (Dysentery); Ibid. 334 (Colic); Ibid. 370 (Stomach aches).	**Sweden**: *18th*: Linnaeus, 1782:72 (Purgative). **England**: *16th–18th*: Gerard, 1597:282; Strother, 1729:64 (Emetic); Hill, 1751:405 (Purgative); Alston, 1770:479 (Cathartic). **France**: *19th*: Loisleur –Deslongchamp, 1819:397; Martin-Lauzer, 1856:462 (Purgative). **Italy**: *16th*: Matthioli, 1568: IV:78 (Staub et al., 2016) (Softens belly, emetic); *19th*: Targioni-Tozzetti, 1847:557 (Induce vomit); Étienne-François, 1756:432; Cassone, 1850:270 (Purgative, emetic).	**Jordan**: Al-Qura'n, 2008:21 (Emetic); Al-Qura'n, 2009:47 (Purgative); Aburjai et al., 2007:298 (Carminative; LF). **Lebanon**: Philips, 1958:259 (Purgative).

		Iraq: *10th-11th*: Ibn Sina, 2012 (vomiting, RT); *11th*: Ibn at-Tilmīd 24 (Kahl, 2007:186) (Stomach pains). **Iran / Iraq**: *9th*: Sābūr ibn Sahl I, 9 (Kahl, 2009:123) (Gastric problems, colic, strengthen the bowels). **Palestine**: *6th*: Asaph IV, 414 **(**Muntner, 1965:396) (Stomach relief). **Egypt**: *Cairo Geniza*: *11th–13th*: Lev, 2007:287 (Stomach ailments).		
Teeth/gum symptom/complaint (D19)	**Ancient Greece**: *1st BCE–1st CE*: Aristoklēs: Keyser and Irby-Massie, 2008:137 (Oral infection).	**Iraq**: *11th*: Ibn at-Tilmīd (Kahl, 2007:186) (Bleeding painful gums).		
Stomach ulcer (D86)		**Iran**: *10th–11th*: Ibn Sina, 1998:225 (Intestinal ulcers). **Iraq**: *11th*: Ibn at-Tilmīd 24 (Kahl, 2007: 187) (Gastric tumors). **Syria / Iraq**: *12th*: Budge, 1913 II:370 (Stomach ulcer).		**Turkey**: Paksoy et al., 2016:5 (Peptic ulcers; RT).
Jaundice (D13; see text)		**Italy**: *9th–12th*: Goehl, 2015:312.		
Liver disease / Liver conditions / Cirrhosis / Bile (D97)	**Ancient Rome**: *1st CE*: Dioscorides IV 75, 3 (Brings up phlegm and bile); Celsus V, 25, 3 (Spencer, 1935:60) (Liver).	**Syria / Iraq**: *12th*: Budge, 1913 II:160 (Pain in the liver, pains in excretory organs); Ibid. II:370,371 (Liver problems and pains).	**Italy**: *18th*: Étienne-François, 1756:432; Tessari, 1762:177 (Cirrhosis).	**Turkey**: Başer et al., 1986:2011 (Stops fever of the bile and blood).
Eye symptoms / complaint (F29)	**Ancient Greece**: *5th BCE*: Hērōn (Keyser and Irby-Massie, 208:384) (Eye problems); *1st CE*: Ptolemaios (Pharm.) (Keyser and Irby-Massie, 2008:703) (Eye ointment). **Ancient Rome**: *1st BCE*: Philoxenos os Alexandria: Keyser and Irby-Massie, 2008:662 (Eye diseases); *1st CE*: Celsus VI, 6, I (Spencer, 1935:191) (Eye problems); Celsus V, 5,3 (Spencer, 1935:60) (Ophthalmia); Galen (Gómez Ortega, 1784b:60) (Eye pain, dilatation of	**England**: *12th–13th*: Gilbertus Anglicus (Handerson, 1918:33). **Spain**: *13th*: Nathan Falaquera (Amar and Buchman, 2004:178) (Eye pain). **Byzantine Empire**: *4th–15th*: Ramoutsaki et al., 2002b:554 (Eye inflammation); *6th–7th*: Thomson, 1995 (in Scarborough, 2010:XIV, 87) (Eye diseases).	**England**: *16th–18th*: Gerard, 1597:282; Dale, 1693:269; Alleyne, 1733:75; James, 1747:365 (Eye problems / diseases); Miller, 1722:284; James, 1747:365 (Eye redness); Culpeper, 1794:263 (Eye pain). **Germany**: *18th*: Weinmann, 1742:348 (Red eyes). **France**: *17th–18th*: Pomet, 1694:135 (Eye inflammation); Alexandere, 1759:286 (Eye redness, eye pain). **Spain**: *16th*: Laguna, 1555:423 (Eye pain, Eye inflammation).	**Iraq**: *Jews*: Ben Yaakov, 1992:165 (Eye problems).

	the pupils); Dioscorides IV. 75, 4 (Compound drug for inflammation of the eye, LF) (Beck, 2017:279); Pliny 25, 147 (König, 1996:100–101; Bonet, 2014:418) (Lacrimation, the secretion of tears, especially when abnormal or excessive; RT, FR).	**Syria / Iraq**: *12th*: Budge, 1913 II:272 (Eye diseases). **Palestine**: *6th*: Asaph IV, 414 (Muntner, 1965:396) (Eye diseases). **Iraq**: *10th–11th*: Ibn Sina, 2012 (visual organs; RT, LF).	**Italy**: *16th*: Matthioli, 1568: IV:78 (Staub et al., 2016) (Eye inflammation); *19th*: Tasso, 1848:167 (Eye problems).	
Ear symptoms (H29) / Ear infection / Earache (H01) / Ear sores		**England**: *11th*: Van Arsdall, 2012:133; *12th*: Black, 2012:133 (Earache). **Spain**: *12th*: Al-Isbili, 2007, II:449 (Sore ears). **Byzantine Empire**: *4th–15th*: Ramoutsaki et al., 2002b:554 (Ulcers in the ear; ear inflammation). **Syria / Iraq**: *12th*: Budge, 1913 II:334 (Earache). **Iraq**: *11th*: Ibn at-Tilmīd (Kahl, 2007:186) (Earache). **Egypt**: *Mamluk Cairo*: *12th–15th*: Chipman, 2010:216 (Earache).	**Italy**: *19th*: Cassone, 1850:269; Zucchi and Ranzoli, 1854:516 (Ear problem).	
Irregular heart beat / Heart disease / Blood flux (K05)		**England**: *12th*: González Blanco, 2018:117 (Controls blood flux). **Syria–Iraq**: *12th*: Budge, 1913 II:334 (Flow of the blood). Ibid. II:503 (Heart diseases).	**Italy**: *19th*: Zucchi and Ranzoli, 1854:516 (Controls blood flux).	
Haemorrhoids / Rectum treatment / Suppository (K96)	**Ancient Greece**: *5th–4th BCE*: Hippocrates, Fist. 9 (Potter, 1995:404–405; Aliotta et al., 2003:212) (Inflammation of the rectum; RT).	**Egypt**: *12th*: Maimonides (Muntner and ben Maimon, 1942:154) (Haemorrhoids).		**Turkey**: Ozturk et al., 2011:202; Fakir et al., 2009 (Haemorrhoids); Başer et al, 1986:2011 (Haemorrhagic piles). **North Africa**: Anonymous, 2005:154 (Haemorrhoids; RT).

Rheumatism (L88) / Joint pain or inflammation (L20) / Hip pain (L13)	**Ancient Greece**: *5th–4th BCE*: Hippocrates, Loc. Hom. 39 (Potter, 1995:78–79; Aliotta et al., 2003:212) (Rheumatism, joint pain). *4th–3rd BCE*: Theophrastus, *Enquiry into Plants* IX, 9.1 (Amigues, 2006:24) (Joint pain). **Ancient Rome**: *1st CE*: Galen (Adams, 1849:814) (Inflammation); Dioscorides IV 75,5 (Beck, 2017:279–280) (Joint pain; RT); Celsus V, 25,3 (Spencer, 1935:60) (Pain in the hips).	**England**: *12th*: Black, 2012:133 (Strained limbs). **Germany**: *8th*: Lorsch pharmacopoeia (Stol, 1992:189) (Joint pain in cold and snow). **Spain**: *13th*: Nathan Falaquera (Amar and Buchman, 2004:178) (Rheumatism). **Iran**: *9th*: Al Razi (Tibi, 2006:207); *13th*: Al-Quzwini (Lev and Amar, 2008:260) (Joints). **Iraq**: *11th*: Ibn at-Tilmīd (Kahl, 2007:187) (Rheumatism). **Syria / Iraq**: *12th*: Budge, 1913 II:93 (Rheumatism pains); Ibid**.** 160 (Joint pain); *12th*: Budge, 1913 II:359 (Painful inflammation). **Egypt**: *12th*: Maimonides (Muntner and ben Maimon, 1942:154) (Rheumatism).	**England**: *18th*: Salmon, 1707:736 (Pain of the joints; rheumatism). **Spain**: *16th*: Laguna, 1555:424 (Joint pain). **Italy**: *16th*: Matthioli, 1568: IV:78 (Staub et al., 2016) (Joint pain); *19th*: Cassone 1850:270 (Rheumatism).	**Greece**: Brussell, 2004:197 (Sore muscles, joints). **Turkey**: Ugulu et al., 2009:361 (Joint pain RT); Başer et al., 1986:2011 (Lumbago, rheumatism). **Iran**: Ziaei et al., 2016:64 (Rheumatism); Ibid. 66 (Joint pain). **Lebanon**: Philips, 1958:259 (Rheumatism). **North Africa**: Anonymous, 2005:154 (Rheumatism, Inflammatory; LF). **Morocco**: El Abbouyi et al., 2014:245; Zakariya et al., 2018:128 (Rheumatism).
Fracture (L76)		**Iraq**: *11th*: Ibn at-Tilmīd (Kahl, 2007:187) (Open fractures).		
Headache / Migraine (N01)	**Ancient Rome**: *1st CE*: Celsus V.25.3 (Spencer, 1935:60) (Headache).	**England**: *12th*: González Blanco, 2018:116 (Migraine). **Spain**: *12th–13th*: Ibn al-Baytar (Leclerc, 1883:419) (Headache). **Italy**: *12th*: Goehl, 2015:311–312 (Headache). Iran / Iraq: *9th*: Sābūr ibn Sahl I.78 (Kahl, 2009:151) (Headache). **Iraq**: *10th–11th*; Ibn Sina (Zargaran et al., 2016:474) (Hot migraine); Ibn at-Tilmīd 21 (Kahl, 2007:184,186). (Headache).	**England**: *16th–19th*: Salmon, 1707:736; James, 1747:365; Culpeper, 1794:264 (Headache). **France**: *18th*: Geoffroy, 1743:4 (Headache). **Italy**: *16th*: Matthioli, 1568:IV:78 (Staub et al., 2016) (Headache). **Serbia**: *15–16th*: Jarić et al., 2011:77; Jarić et al., 2014:1366 (Headache). **Turkey**: *Anatolia*: *15th*: Ganidagli et al., 2004:167 (Headache).	**Turkey**: Başer et al., 2011:986 (Headache). **Iran**: Bayan et al., 2013:120 (Headache).

		Syria / Iraq: *12th*: Budge, 1913 II:334 (Headache). **Egypt**: *Mamluk Cairo*: *12th–15th*: Chipman, 2010:267 (Migraine).		
Convulsions / Antispasmodic (N07)	**Ancient Greece**: *5th–4th BCE*: Hippocrates, Loc. Hom. 39 (Potter, 1995:79) (Convulsions, RT); *1st CE*: Terentius Valens (Keyser and Irby-Massie, 2008:774) (Antispasmodic).	**England**: *12th*: González Blanco, 2018:116 (Smooth convulsions). **Byzantine Empire**: *2nd–4th CE*: Ramoutsaki et al., 2002a:44 (Antispasmodic). **Syria / Iraq**: *12th*: Budge, 1913 II: 334 (Gripping; convulsions). **Egypt**: *12th*: Maimonides (Muntner and ben Maimon, 1942:154) (Antispasmodic).	**Sweden**: *18th*: Linnaeus, 1782:72 (Antispasmodic). **England**: *19th*: Woodville, 1832:236 (Antispasmodic). **Italy**: *18th–19th*: Étienne-François, 1756:432; Cassone, 1850:269 (Convulsions).	**Iran and Arabia**: Ainslie, 1826 I: 207 (Antispasmodic)**.** **North Africa**: Anonymous, 2005:154 (Antispasmodic; RT, LF).
Epilepsy, Nerve diseases (N88)		**England**: *11th*: Van Arsdall, 2012:133 (Nerve spasm); *12th*: Black, 2012:133 (Epilepsy). **Iraq**: *9th*: Al Kindi No. 205 (Lev, 2012:130); Levey, 1966b:330 (Epilepsy). **Egypt**: *Cairo Geniza*: *11th–13th*: Lev, 2007:287 (Epilepsy); *Mamluk Cairo*; *12th–15th*: Chipman, 2010:167 (Epilepsy).	**England**: *18th*: Alston, 1770 I: 479 (Epilepsy) (Recommended for epilepsy). **Sweden**: *18th*: Linnaeus, 1782:72 (Epilepsy). **France**: *19th*: Loisleur-Deslongchamp, 1819:397; Bouillet, 1874:1024 (Epilepsy); Martin-Lauzer, 1856:462 (Nerve diseases). **Italy**: *18th–19th*: Étienne-François, 1756:432; Cassone, 1850:269 (Epilepsy).	
Paralysis (N91)		**Egypt**: *Mamluk Cairo: 12th–15th*: Chipman, 2010:267 (Hemiplegia, facial paralysis).		
Sleep disturbance / Sleep disorders / Anti-insomnia / Somnolent / Soporific (P06)	**Ancient Greece**: *4th–3rd BCE*: Theophrastus, *Enquiry into Plants* IX, 9.1 (Amigues, 2006:24) (Sleeping; RT). **Ancient Rome**: *1st CE*: Celsus V.25.2 (Spencer, 1935:61) (Insomnia); Celsus III, 18.12 (Spencer, 1935:295) (Insomnia); Dioscorides IV 75, 3 (Beck, 2017:279) (Soporific; FR, RT), IV 75, 5 (Beck,	**England**: *12th*: González Blanco, 2018:116 (Facilitates sleep); *12th–13th*: Gilbertus Anglicus (Handerson, 1918:64) (Sleeping); *15th*: González Blanco, 2018:117 (Facilitates sleep). **Germany**: *8th*: Lorsch pharmacopoeia (Stol, 1992:347) (Induces sleep).	**England**: *16th–18th*: Gerard, 1597:282; Parkinson, 1629:378; Hill, 1751:405 (Sleep); Renou, 1657:345; Dale, 1693:269; James, 1747:365 (Soporific); Culpeper, 1794:263 (Suppository to cause sleep). **Netherlands**: *16th*: Ostling, 2016:65) (Induces sleep).	**Turkey**: Mert et al., 2008:833 (Soporific). **North Africa**: Boulos, 1983:167 (Soporific; RT).

	2017:280) (Losing consciousness); Pliny, 25, 149 (Bonet, 2014:418) (Insomnia).	**Spain**: *12th–13th*: Ibn al-Awwam (Banqueri, 1812:491) (Soporific); Ibn al-Baytar (Leclerc, 1883:419) (Sleep inducer, against insomnia); *13th*: Nathan Falaquera (Amar and Buchman, 2004:178) (Soporific); *14th*: Armengaud Blaise No. 64 (Mcvaugh and Ferre, 2000:149) (Soporific, against wakefulness). **Italy**: *9th–12th*: Goehl, 2015:312 (Sleeping); 12th: Platerius (Goehl, 2015:311–312) (Induces sleep). **Byzantine Empire**: *5th*: Macrobius VII, 6, 7 (Randolph, 1905:510) (Insomnia); *7th*: Paul of Aegina V, 49 (Adams, 1861:218) (Soporific). **Iran**: *10th–11th*: Al-Bīrūnī (Tschanz, 1997:4) (Soporific). **Syria / Iraq**: *10th-11th*: Ibn Sina, 2012 (Sleep producing, hypnotic, RT); *12th*: Budge, 1913 II:503,713 (Sleeping); Ibid. 674 (Insomnia). **Iraq**: *11th;* Ibn at-Tilmīd 21 (Kahl, 2007:184) (Insomnia). **Egypt**: *Mamluk Cairo*: *12th–15th*: Chipman, 2010:265 (Soporific).	**Germany**: *16th–18th*: Fuchs, 1542:610 (Suppository for sleep); Weinmann, 1742:349 (Soporific). **France**: *17th*: Pomet, 1694:135 (Causes sleep). **Spain**: *16th*: Laguna, 1555:423 (Causes sleep, soporific); *18th*: Gómez Ortega, 1784a:401 (Somnolent); Laza Palacios, 1953:166 (Soporific). **Italy**: *16–18th*: Matthioli, 1568: IV:78 (Staub et al., 2016); Étienne-François, 1756:432; Targioni-Tozzetti, 1847:557 (Soporofic); Zucchi and Ranzoli, 1854:516 (Sleep inducer). **Serbia**: *15th–16th*: Jarić et al., 2014:1366 (Encourages sleep).	
Feeling anxious / Sedative / *Anxiety* (P74) / Tranquilliser (P01)	**Ancient Greece**: *5th—4th BCE*: Hippocrates, Loc. Hom. 39 (Potter, 1995:78–79; Aliotta et al., 2003:212) ("Those who are troubled and ill"; i.e., sedative; RT); *1st CE*: Iulius Bassus (Keyser and Irby-Massie, 2008:45) (Sedative).	**Spain**: *7th*: Isidore of Seville (Barney et al., 2006:351) (Sedative). **Byzantine Empire**: *2nd–4th*: Ramoutsaki et al., 2002a:44 (Sedative)**.** **Syria / Iraq**: *12th*: Budge, 1913 II:503 (Sedative, Continuous fear).	**Italy**: *19th*: Zucchi and Ranzoli, 1854:516 (Sedative). **Serbia**: *15th–16th*: Jarić et al., 2011:77 (Sedative).	**Turkey**: Mert et al., 2008:833 (Tranquilliser). **Jordan**: Aburjai et al., 2007:298; Oran and Al-Eisawi, 2015:386 (Sedative; LF) **North Africa**: Boulos, 1983:167 (Sedative; RT).

				Morocco: Merzouki et al., 2000:302 (Sedative; RT).
Psychological symptoms (P29) / Depression (P76) / Melancholy / Phlegm (psychological)	**Ancient Greece**: *5th–4th BCE*: Hippocrates, Loc. Hom. 39 (Aliotta et al., 2003:212) (Melancholy); *1st–2nd CE*: Galen (Adams, 1849:77) (Treats suicidal mania).	**England**: *12th*: González Blanco, 2018:116 (Purges phlegm). **Spain**: *12–13th*: Ibn al-Baytar (Leclerc, 1883: 419) (Mental alienation).	**Sweden**: *18th*: Linnaeus, 1782:72 (Hysteria). **England**: *15th*: González Blanco, 2018:116 (Against weariness; purges phlegm); *18th*: Salmon, 1707:736 (Madness); Strother, 1729:64 (Relax); Hill, 1751:405 (Hysteria); Culpeper, 1794:263 (Purges phlegm and melancholy). **Spain**: *16th*: Laguna, 1555:423 (Purges phlegm and melancholy). **Italy**: *19th*: Zucchi and Ranzoli, 1854:516 (Fatigue).	**England**: Woodville, 1832:236 (Melancholy).
Psychological disorders (P99): Madness / Insanity / Hysteria	**Ancient Greece**: *5th–4th BCE*: Hippocrates, Loc. Hom. VI, 39.102 (Aliotta et al., 2003:212) (Insanity). **Ancient Rome**: *1st CE*: Celsus V, 25, 3 (Spencer, 1935:60) (Collapse speechless, hysteria).	**England**: *11th*: Van Arsdall, 2012:133 (Insanity). **Iraq**: *9th*: Al Kindi no. 189 (Lev, 2012:130); Levey, 1966b:330 (Cures insanity). **Egypt**: *Cairo Geniza: 11th–13th*: Lev and Amar, 2008:213; Lev, 2007:287 (Insanity); *Mamluk Cairo: 12th–15th*: Chipman, 2010:167 (Madness).	**France**: *19th*: Loisleur –Deslongchamp, 1819:397 (Hysteria). **Italy**: *19th*: Zucchi and Ranzoli, 1854:516 (Mental problems); Cassone, 1850:269; Zucchi and Ranzoli, 1854:516 (Cures nervous system); Cassone, 1850:269 (Hysteria).	
Respiratory symptoms / *Asthma* (R96) / *Bronchitis* (R78-R79)	**Ancient Greece** *1st BCE–1st CE*: Kharïxenēs (Keyser and Irby-Massie, 2008:471) (Respiratory affections); *1st CE*: Kharixenēs (Keyser and Irby-Massie, 2008:471) (Respiratory problems). **Ancient Rome** *1st CE*: Celsus V, 25,3 (Spencer, 1935:60) (Difficulty breathing).	**Spain**: *12th–13th*: Ibn al-Baytar (Leclerc, 1883:419) (Suffocation). **Syria / Iraq**: *12th*: Budge, 1913 II:274 (Chest disease); Ibid. II, 503 (Respiratory problems). **Iraq**: *11th*: Ibn at-Tilmīd 24 (Kahl, 2007:186) (Expectoration).	**Serbia**: *15 th–16 th*: Jarić et al., 2011:77 (Lung diseases).	**Cyprus**: González-Tejero et al., 2008:352 (Respiratory). **Jordan**: Aburjai et al., 2007:298 (Bronchitis; LF). **North Africa**: Boulos, 1983:167 (Bronchitis; LF). **Morocco**: Bnouham et al., 2006:26 (Asthma; RT, LF).
Cough / Cold (R05)	**Ancient Greece**: *1st BCE–1st CE*: Kharïxenēs (Keyser and Irby-Massie, 2008:471 (Cough); *1st CE*: Flauianus of	**England**: *12th*: González Blanco, 2018:116 (Cold).	**England**: *15th*: González Blanco, 2018:116 (Cold).	**Jordan**: Aburjai et al., 2007:298; Oran and Al-Eisawi, 2015:386 (Cold; LF).

	Crete (Keyser and Irby-Massie, 2008:329) (Component in cough drops).	**Byzantine Empire**: *4th–15th*: Ramoutsaki et al., 2002b:554 (Cough). **Iraq**: *11th*: Ibn at-Tilmīd (Kahl 2007:186) (Cough). **Syria / Iraq**: *12th*: Budge 1913 II:257 (Cough).	**Serbia**: *15 th–16th* Jarić et al., 2011:77 (Cold).	**Cyprus**: Lardos, 2006:389 (Cold; LF, RT). **North Africa**: Boulos, 1983:167 (Cough, throat pain; LF). **Morocco**: Bnouham et al., 2006:26 (Cold; RT, LF).
Haemoptysis / Phthitis (Tuberculosis) / Bloody cough (R24)	**Ancient Rome**: *1st BCE*: Krateros of Antioch (Keyser and Irby-Massie, 2008:489) (Phthitis, tuberculosis and blood spitting); *1st CE*: Abaskantos of Lungdunum (Keyster and Irby-Massie, 2008:29) (Phthitis). **Ancient Rome**: *1st BCE–1st CE*: Kharïxenēs (Keyser and Irby-Massie, 2008:471) (Blood spitting and cough).	**Iraq**: *10th–11th*: Ibn Sina, 2012 (Coughing up blood, tuberculosis; RT); *11th*: Ibn at-Tilmīd 24 (Kahl, 2007:186) (Bloody expectoration).	**Italy**: *19th*: Zucchi and Ranzoli, 1854:516 (Tuberculosis).	
Nose bleed / *epistaxis* (R06)		**Iran**: *10th–11th*: Ibn Sina 1998:225 (Nasal bleeding).		
Inflammation (S87) / *Tumor* (S04-S77) / *Swelling* (S04) / Ulcers (S97) / Abscess / Scrofula / Struma / Oedema / Adenoma / Cancer ulcer	**Ancient Greece**: *5th–4th BCE*: Hippocrates (Adams, 1849:822) (Inflamed fistulae); *4th–3rd BCE*: Theophrastus, *Enquiry into Plants* IX, 9.1 (Amigues, 2006:24) (Ulcers; LF); *3rd BCE–1st CE (?)*: Erasistratos of Sikuōn (Keyster and Irby-Massie, 2008:297) (Blisters); *2nd–1st BCE*: Philoxenos of Alexandria (Keyser and Irby-Massie, 2008:662) (Tumors). **Ancient Rome**: *1st CE*: Dioscorides IV 75, 4: (Beck, 2017:279) (Inflammation of sores and abscesses; LF); Pliny 26, 24 (Bonet, 2014:418) (Tumor; LF); Pliny 26,154 (Bonet, 2014:418) (Abscess; LF); Pliny 26, 93 (König, 1983:70–71) (Swollen glands); Pliny 26, 145 (König, 1983:102–103) (Abscess); Celsus V, 25.3 (Spencer, 1935:60) (Ulceration).	**England**: *12th*: Black, 2012:133 (Swelling)**.** **Germany**: *8th*: Lorsch pharmacopoeia (Stol, 1992:354–355) (Tumors). **Iran / Iraq**: *9th*: Sābūr ibn Sahl I.101 (Kahl, 2009:156) (Ulcers). **Iraq**: *10th-11th*: Ibn Sina, 2012 (inflammation, pustules; RT); *11th*: Ibn at-Tilmīd (Kahl, 2007:187) (Burns, swellings, tumors, ulcers, abscesses). **Syria / Iraq**: *12th*: Budge, 1913 II: 359 (Painful inflammation); Budge, 1913 II: 684 (Ulcers).	**Sweden**: *18th*: Linnaeus, 1782:72 (Tumor). **England**: *18th–19th*: Miller, 1722:284 (Scrofulous swellings); Culpeper, 1794:263 (Ulcers, swellings and inflammations); Gerard, 1597:282; Alston, 1770 I:479; Quincy, 1782:489 (Inflammation); Redwood, 1857:416 (Indurable glands; LF); James, 1747:365; Hill, 1751:405; Alston, 1770 I:487 (Swelling); Dale, 1693:269; James, 1747:365 (Struma); Dale, 1693:269; James, 1747:365; Swediaur, 1786:128 (Scrofula); Dale, 1693:269; Woodville, 1832:236 (Tumor); James, 1747:365 (Hard tumor). **France**: *17th–19th*: Geoffroy, 1743:4; Martin-Lauzer, 1856:462; Milne-Edwards and Vavasseur, 1831:208 (Tumors); Loisleur –Deslongchamp, 1819:397; Pomet, 1694:135; Alexandere, 1759:286 (Scrofulous tumors); Loisleur –	**Italy:** Tuttolomondo et al., 2014:578 (Pimples). **Turkey:** Ugulu et al., 2009:361 (Anti-inflammatory; RT).

			Deslongchamp, 1819:397 (Cancer); Pomet, 1694:395 (Breast cancer); Geoffroy, 1743:4 (Inflammation). **Germany**: *17th–19th*: Weinmann, 1742:349 (Inflammation); Schröder, 1685:622; Weinmann, 1742:348; Geiger, 1839:568 (Scrofula); Schröder, 1685:622; Goeschen, 1868:228 (Struma); Goeschen, 1868:228 (Abscess); Geiger, 1839:568 (Swelling). **Italy**: *16th*: Matthioli, 1568: IV:78 (Staub et al., 2016) (Scrofulous swelling of glands, abscesses, abscesses caused by ulcers, scars); *18th–19th*: Tasso, 1848:167 (Inflammations); Tasso, 1848:167 (Tumor, scrofula); Étienne-François, 1756:432 (Inflammations); Cassone, 1850:270 (Indurable glands, gland inflammations); Zucchi and Ranzoli, 1854:516 (Glandular infections); Étienne-François, 1756:432 (Struma); Étienne-François, 1756:432 (Tumor); Cassone, 1850:270 (Hard tumors). **Spain**: *16th*: Laguna, 1555:423 (Sores, ulcers, hardness); *19th*: Pontesy Rosales, 1878:279 (Tumor, scrofula). **Serbia**: *15th–16th*: Jarić et al., 2014:1366 (Swelling). **Palestine**: *16th–17th*: Hayyim Vital (Buchman and Amar, 2004:199) (To dissolve tumors).	
Skin problems / Wounds (S16-S19) / Sores / Warts (S03) / Erysipelas / Chilblains / Skin problems (or as emollient, desiccative, resolvent)	**Ancient Greece**: *4th–3rd BCE*: Theophrastus, *Enquiry into Plants* IX, 9.1 (Amigues, 2006:24) (Erysipelas; RT, LF), Ibid. (Wounds; RT, LF); 3rd *BCE–1st CE (?)*: Erasistratos of Sikuōn (Keyster and Irby-Massie, 2008:297) (Blisters). **Ancient Rome**: *1st CE*: Pliny: 26, 121 (König, 1983:76–79) (Erysipelas; RT); Pliny, 26, 145 (Bonet, 2014:418) (Wounds; RT); Pliny 25, 175	**Spain**: *12th–13th*; Ibn al-Baytar (Leclerc, 1883: 419) (Redness of the face). **Byzantine Empire**: *4th–15th* CE: Ramoutsaki et al., 2002b:554 (Plaster). **Iran / Iraq**: *9th*: Sābūr ibn Sahl I.101 (Kahl, 2009:156). (Cataplasm).	**England**: *17th–19th*: Dale, 1693:269; Alleyne, 1733:75; James, 1747:365 (Erysipelas); Hill, 1751:405 (Emollient); Culpeper, 1794:264 (Wound); Woodville, 1832:236 (Cataplasm). **Netherlands**: *17th*: Boerhaave, 1755:171 (Ointment, cataplasm). **Belgium**: *19th*: Nysten, 1840:522 (Cataplasm).	**Spain**: Guzmán, 1997:442; Casado, 2003:227 (Chilblains; LF). **Italy**: Leto et al., 2013:102 (Skin boils, cataplasm; LF); Tuttolomondo et al., 2014:578 (Warts, wounds).

	(König, 1996:118–119) (Facial cicatrix, scars, RT); Pliny 26, 149 (König, 1983:104–105) (Removes objects from the body).	**Iraq**: *10th–11th*: Ibn Sina, 2012 (freckles, swellings, abscesses; LF); *11th*: Ibn at-Tilmīd (Kahl, 2007:187) (Frostbite of hands and feet). **Syria / Iraq**: *12th*: Budge, 1913 II: 272 (Wounds, skin, excessive pus). **Palestine**: *6th*: Assaph IV, 414 (Muntner 1965:396) (Skin disease); Ibid. 415 (Stops bleeding). **Egypt**: *Cairo Geniza*: *11–13th*: Lev, 2007:287 (Skin problems, skin diseases).	**Germany**: *17th*: Schröder, 1685:622 (Emollient); Schröder, 1685:622; Weinmann, 1742:348 (Erysipelas). **France**: *17th–19th*: Pomet, 1694:135; Alexandere, 1759:286 (Erysipelas); Milne-Edwards and Vavasseur, 1831:298 (Poultice); Alexandere, 1759:286 (Emollient); Alexandere, 1759:286 (Desiccative); Pomet, 1694:395; Alexandere, 1759:286; Bouillet, 1874:1024 (Cataplasm); Geoffroy, 1743:4 (Resolvent). *18th–19th*: Geoffroy, 1743:4 (Erysipelas); Martin-Lauzer, 1856:462 (Cataplasm). **Spain**: *16th*: Laguna, 1555:424 (Erysipelas: Saint Anthony's Fire); *19th*: Pontesy Rosales, 1878:743 (Cataplasm). **Italy**: *16th*: Matthioli, 1568:IV:78 (Staub et al., 2016) (Indurations, erysipelas, Saint Anthony's Fire); *18th–19th*: Étienne-François, 1756:432 (Resolvent); Étienne-François, 1756:432 (Emollient): Tasso, 1848:167; Cassone, 1850:270; (Cataplasm): Étienne-François, 1756:432 (Skin).	**Cyprus**: González-Tejero et al., 2008:352; Lardos, 2006:389 (Skin conditions); Lardos, 2006:389 (Wounds; LF, RT). **Turkey**: Ozturk et al., 2011:202 (Antidermatosis). **Jordan**: Al-Qura`n, 2009:47 (Ointments).
Animal bites: Snake / Scorpion / Insect (S12-S13)	**Ancient Rome**: *1st CE*: Dioscorides IV, 75, 5 (Beck, 2017: 279–280) (Snake bites, RT); Pliny 25, 150 (Bonet, 2014:418); Pliny 26, 104–105 (König, 1983:76–79) (Snake bites). **Ancient Iran**: *3rd CE*; Sābŭr ibn Sahl (Chipman and Lev, 2008:378) (Animal bites and stings).	**Spain**: *13th*: Nathan Falaquera (Amar and Buchman, 2004:178) (Scorpion sting). Iran / Iraq: *9th*: Sābūr ibn Sahl I.9 (Kahl, 2009:123) (Stinging animals). **Syria / Iraq**: *12th*: Budge, 1913 II:408 (Insect bites). **Iraq:** *10th-11th*: Ibn Sina 2012 (Insect bites; LF). **Palestine**: *6th*: Assaph IV, 414 (Muntner, 1965:396) (Snake and scorpion bites).	**Spain**: *16th*: Laguna, 1555:424 (Snake bites). **Italy**: *16th*: Matthioli, 1568: IV:78 (Staub et al., 2016) (Snake bites).	

		Egypt: *12th*: Maimonides (Muntner and ben Maimon, 1942:104, 109) (Snake bites).		
Gout (T92) / Arthritis / Podagra	**Ancient Greece**: *3rd BCE–1st CE* (?): Erasistratos of Sikuōn (Keyster and Irby-Massie, 2008:197) (Gout). **Ancient Rome**: *1st CE*: Pliny 26, 104–6 (Bonet, 2014:418) (Gout); Pliny 26, 104–105 (König, 1983:76–79) (Arthritis).	**Germany**: *8th*: Lorsch pharmacopoeia (Stol, 1992:354–355) (Gout). **Syria / Iraq**: *12th*: Budge, 1913 II:160 (Gout). **Iraq**: *10th-11th*: Ibn Sina 2012 (Arthritis; RT); *11th*: Ibn at-Tilmīd (Kahl, 2007:187) (Gout).	**Sweden**: *18th*: Hoffberg, 1763:231 (Gout); Linnaeus, 1782:72 (Podagra). **England**: *11th*: Van Arsdall, 2012:133 (Gout); *12th*: Black, 2012:133; Salmon, 1707:736 (Gout). **France**: *19h*: Loisleur-Deslongchamp, 1819:397 (Gout). **Italy**: *19th*: Cassone, 1850:270 (Arthritis, Gout).	
Loss of appetite / Appetizer (T03)		**Spain**: *12th–13th*: Ibn al-Baytar (Leclerc, 1883:419) (To get fat).		**Turkey**: Paksoy et al., 2016:5 (Appetizing; RT). **North Africa**: Boulos, 1983:167 (Increases weight of women; RT). **Morocco**: Bnouham et al., 2006:26 (Appetizing; RT, LF).
Urinary symptoms (U29) / *Kidney symptoms* (U14)		**England**: *12th*: González Blanco, 2018:116 (Destroys kidney stone). **Syria / Iraq**: *12th*: Budge, 1913 II:408 (Painful urination).	**England**: *15th*: González Blanco, 2018:116 (Destroys kidney stones). **Germany**: *16th*: Rosenberg, 1930:675 (Kidney and bladder). **Italy**: *15th*: Cassone, 1850:270 (Urinary stones).	**Turkey**: Başer et al., 1986:2011 (Bed-wetting by children, inflammation of the urethra). **Morocco**: Benkhnigue et al., 2016:44 (Urinary infection).
Abortion / *Unwanted pregnancy* (W79) / *Complicate labour* (W92)	**Ancient Greece**: *1st BCE–1st CE*: Arninas of Indos (Keyser and Irby-Massie, 2008:124) (Abortive). **Ancient Rome**: *1st CE*: Dioscorides IV 75, 4 (Beck, 2017:279) (causes foetus "to move"; RT, FR); Pliny 26, 156 (Bonet, 2014:418) (Expels dead foetus).	**Spain**: *13th*: Nathan Falaquera (Amar and Buchman, 2004:178) (Abortion). **Iraq**: *10th–11th*: Ibn Sina, 2012 (abortive; RT). **Egypt**: *Mamluk Cairo: 12th–15th*: Chipman, 2010:167 (Expels foetus and infant).	**Sweden**: *19th*: Linnaeus, 1782:72 (Abortive). **England**: *16th–18th*: Culpeper, 1794:263 (Brings forth dead child); Forman (Traister, 1991:446) (Discharges stillbirth, purifying). **Germany**: *16th*: Lonicerus, 1582:195 (Expels foetuses, dead or alive).	

			Spain: *16th*: Laguna, 1555:423 (Induces abortion). **Italy**: *16th*: Matthioli, 1568: IV:78 (Staub et al., 2016) (Expels embryo/ foetus); *18th*: Étienne-François, 1756:431 (Barren woman, Uterus); Tessari, 1762:177 (Abortive).	
Subfertility / Aphrodisiac / Philtre (W15)	**Bible:** Genesis 30: 4–16. **Ancient Greece**: *4th–3rd BCE*: Theophrastus, *Enquiry into Plants* IX, 9.1 (Amigues, 2006:24) (Aphrodisiac; RT). **Ancient Rome**: *1st CE*: Dioscorides IV 75, 1 (Beck, 2017:278) (Aphrodisiac; RT). **Ancient Iran**: *3rd CE*: Sābŭr ibn Sahl (Chipman and Lev, 2008:378) (Fertility).	**Egypt**: *Mamluk Cairo*: *12th–15th*: Chipman, 2010:168 (Aphrodisiac); Ibid. 167 (Love, male fertility).	**Spain**: *18th*: Quer, 1762:7 (Against sterility). **Italy**: *16th–19th*: Matthioli, 1568 IV:78 (Staub et al., 2016); Targioni-Tozzetti, 1847:557 (Aphrodisiac); Étienne-François, 1756: 431 (Fertility).	**England**: Redwood, 1857:416 (Fertility; RT). **Spain**: Ortuño, 2003:173 (Sexual stimulant). **Turke**y: Mert et al., 2008:833; Everest and Ozturk, 2005:2 (Aphrodisiac; RT). **Armenia**: Russel, 1987:92 (Love potion). **Iraq**: *Jews*: Ben–Yaakov, 1992:262 (Aphrodisiac). **Lebanon**: Philips, 1958:259 (Aphrodisiac). **Morocco**: Merzouki et al., 2000:302; Ouarghidi et al., 2013:9; Zakariya et al., 2018:128 (Aphrodisiac; RT).
Gynaecology / Female troubles / *Menstruation absence* (X05*) / Vaginal* discharge (X14) / Genital symptom/ *complicated female oth* (X29)	**Ancient Greece**: *5th–4th BCE*: Hippocrates, Morb. Mul I, 74 (Littré, 1853:160–161; Aliotta et al., 2003:212) (Induces menstruation, emmenagogue); Ibid. Mul I, 80 (Littré, 1853:202–203; Aliotta et al., 2003:212) (Cleanses the uterus; eases menstrual symptoms); Ibid. II, 199 (Littré, 1853:382–383; Aliotta et al. 2003:212) (Vaginal discharge).	**Spain**: *13th*: Nathan Falaquera (Amar and Buchman, 2004:178) (Cleans the womb). **Iraq**: *10th–11th*: Ibn Sina, 2012 (uterus cleanup; LF; stop excessive bleeding; RT).	**England**: *16th–18th*: Gerard, 1597:282 (Female fertility); Culpeper, 1794:264 (Cleanses the womb). **Germany**: *16th*: Lonicerus, 1582:195 (Induces menses). **Spain**: *16th*: Laguna, 1555:423 (Softens the uterus, induces menstruation).	**England**: Redwood, 1857:416 (Birth problems; RT). **Jordan**: Aburjai et al., 2007:299 (Genital organ diseases LF). **North Africa**: Boulos, 1983:167 (Diseases of genital organs; LF).

	Ancient Rome: *1st CE*: Dioscorides IV 75, 4 (Beck, 2017:279) (Emmenagogue; RT, FR); Ibid. 280 (Cleanses uterus); Pliny 26, 156–157 (König, 1983:110–111) (Cleanses the uterus); Celsus V, 25,3 (Spencer, 1935:60) (Inflammation of the womb); Celsus V, 25.3 (Spencer, 1935:60) (Genital trouble).		**Italy**: *16th*: Matthioli, 1568: IV:78 (Staub et al., 2016) (Induces menstruation, red vaginal discharge, purges uterus). **Serbia**: *15th–16th*: Jarić et al., 2011:77; Jarić et al., 2014:1366 (Gynaecological conditions).	
Syphilis / Venereal diseases (Y70)		**Spain**: *15th*: Lopez De Villalobos, 1498 (Syphilis).	**England**: *19th*: Bates, 1870:11 (Syphilis); Swediaur, 1786:70 (Induration of the testicle). **Germany**: *19th*: Kosteletzky, 1834:114 (Syphilis).	

* Anaesthetic uses were classified under A01 arranged in a separate row

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Supplementary materials

Supplementary Table A. Main alkaloids and compounds in *Mandragora*. L-hyoscyamine (1), scopolamine (=hyoscine) (2), atropine (3), cuscohygrine (4), apoatropine (5), 3α-tigloyloxytropane (6), 3,6-ditigloyloxytropane (7), β- belladonnine (8), scopine (9), tropine (10), calystegines (11): calystegine A3 (R^1=OH, R^2=H, R^3=H), calystegine B1 (R^1=OH, R^2=H, R^3=OH), calystegine B2 (R^1=OH, R^2=OH, R^3=H), coumarins (12): herniarin (R= 0-CH3), umbelliferon (R= OH), withanolides: mandragorolide A (13), mandragorolide B (14).

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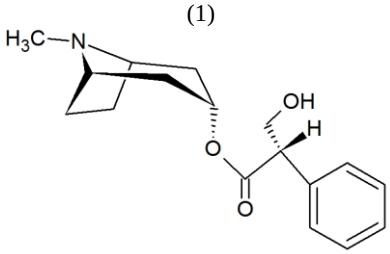

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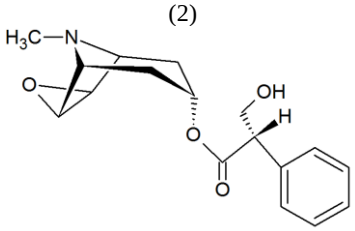

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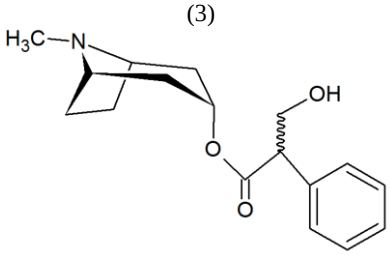

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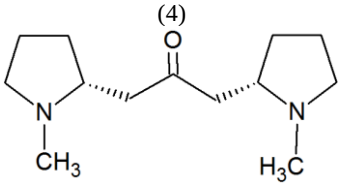

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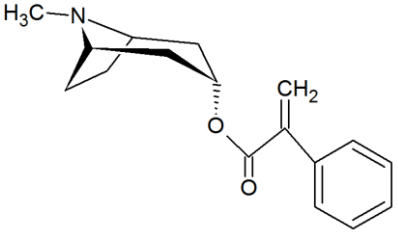

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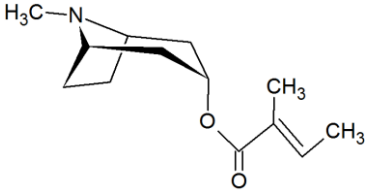

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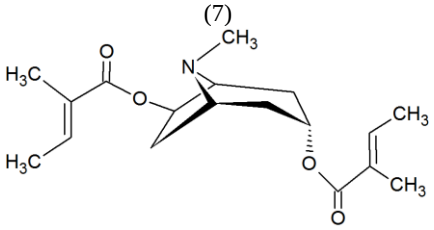

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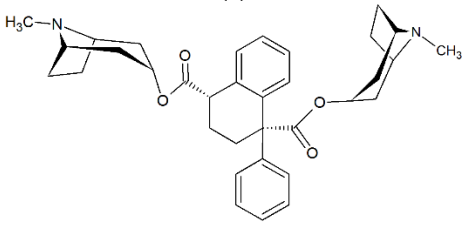

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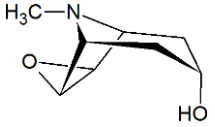

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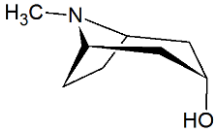

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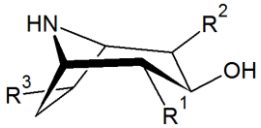

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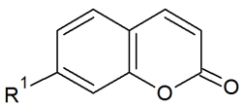

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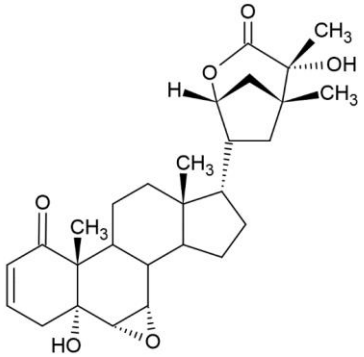

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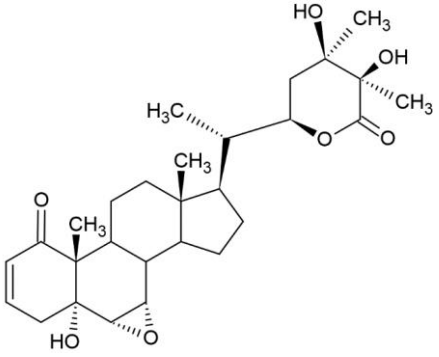

Supplementary Table B. Temporal distribution of uses. In gray uses maintained during the four periods; blue for uses cited in three periods, green for uses in two periods and pink for uses in a single period.