Ca' Granda, *Hortus simplicium*: medicinal species for the treatment of upper airways disorders during the XV-XIX centuries

Martina Bottoni, Fabrizia Milani, Paolo M. Galimberti, Claudia Giuliani and Gelsomina Fico

Correspondence

Martina Bottoni[1,2,†], Fabrizia Milani[1,2,†,*], Paolo M. Galimberti[3], Claudia Giuliani[1,2], and Gelsomina Fico[1,2]

[1]Department of Pharmaceutical Sciences, University of Milan, Via Mangiagalli 25, 20133 Milan, Italy
[2]Ghirardi Botanic Garden, Department of Pharmaceutical Sciences, University of Milan, Via Religione 25, 25088 Toscolano Maderno, Italy
[3]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 28, 20122 Milan, Italy

[†]These authors have contributed equally to this work.

[*]Corresponding Author: fabrizia.milani@unimi.it

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Research

Abstract

Background: This work represents the study of one of the 150 pharmacy jars belonging to the Ospedale Maggiore Ca' Granda in Milan (Lombardy, Italy). This collection is the surviving part of the 450 maiolica jars produced during the XVII and the XVIII centuries and originally preserved in the Pharmacy of the Hospital. Our main objective was the thorough study of the jar number 9 and the remedy once preserved therein from a historical, pharmacological, and phytochemical point of view. This remedy, known as *Electuarium Diacurcumae*, was once used for the treatment of several different pathologies, such as upper airways disorders.

Methods: The following phases were therefore carried out: (i) analysis of the inscription on the jar, with extensive survey on historical medical texts and almanacs to identify the plant-based ingredients of the remedy and its historical medicinal purpose; (ii) bibliographic research in modern scientific literature to validate or refute the historical use of the remedy.

Results: The research highlighted that at least 9 out of the 18 plant-based ingredients of the *Electuarium* would have effectively brought benefit in the treatment of several inflammation-based airways disorders.
Conclusions: Through this multidisciplinary approach, it was possible to underline not only the historic-artistic significance of the jar, but also the potential scientific role of the content.

Keywords: *Hortus simplicium*; ethnobotany; ethnopharmacology; medicinal plants; *Electuarium Diacurcumae*; respiratory tract

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Background

The Ospedale Maggiore of Milan and its collection of pharmacy jars

The wonderful collections of ancient pharmacy furnishings, other than being fascinating for the artistic quality of the maiolica jars, are also important historical remnants of the process of manufacturing and distribution of the ceramic itself. They also provide clues to the production, commercial distribution, and consumption of the medicinal products they contained (Ausenda 2008, Nepoti 2008). These products were identified by inscriptions located on the jars. These inscriptions were always abbreviated and were often written using obsolete script, in order to conceal the content of the jar from the laymen. The collection of the Ospedale Maggiore of Milan cannot compete with others in both richness and largeness. It does, however, represent a unique case for its age and for the network of relations that link its archive, bibliographic, and iconographic sources. The ancient Pharmacy had great interiors and laboratories that unfortunately did not survive the WWII bombings of 1943, with only pictures of the time as evidence. Several items did survive the destruction, including 150 maiolica jars, bronze mortars, and some peculiar objects, such as the "*cassetta delle vipere*" (vipers' box). These surviving artifacts have great value for several reasons. First, archive documents show purchase details of the items and the preparations they contained. The therapeutic uses of these preparations were well described in the pharmacopoeias. Finally, both the area in which the medicinal plants were cultivated, and the corresponding layout plans survived until today. In 1475 the first inventory of the Pharmacy was carried out. A series of end-of-the-year overstock lists survived to this day and were originally compiled between 1558 and 1623. These lists mentioned over 800 ingredients and remedies. The first decision to build a pharmacy inside the Hospital was in 1487, "*a risparmio di spesa e a maggior vantaggio dei malati*". This means that the decision would entail great savings that were passed on to the patients, because it would allow the Pharmacy to drop all its external suppliers. However, the decision didn't take a fact until June 2nd, 1497, when construction on an expansion was completed (Bascapè 1934, Canetta 1884, Castelli 1940, Pecchiai 1927, Sironi 2007). We don't know what kind of furnishings were used during the first 170 years, but we can easily speculate that a big part of this collection was composed of reusable (*i.e.,* tin, pewter, copper, and glass) and perishable (*i.e.*, wood and leather) materials. In addition, it is well known that Hispanic-Moorish maiolicas (sold in Mallorca, hence their name) were already imported goods even since the XIV century. The first representation of a bas-relief zaffar *albarello* made its appearance in a Milanese miniature during the late XIV century. This miniature illustrated the heading *Oleum amigdalarum* of *Theatrum sanitatis casanatense* (Bovi & Capparoni 2001, Galiberti & Perin 1994, Pesce 1972, Scerrato 1991). Five jars made of Tuscan ceramic (possibly from Siena) and that displayed the symbol of the Hospital were made during the first half of 1500 and were most likely part of a much larger group. Of these, two are preserved in the Castello Sforzesco museums of Milan. Both items were donated to the museums by the physician Malachia de Cristoforis in 1876 (https://www.lombardiabeniculturali.it/). A third marked jar is preserved at the Fitzwilliam Museum of Cambridge and dates back to 1541 (https://collection.beta.fitz.ms/id/object/48323). Finally, two jars with the symbol of the Hospital were once preserved at the Museum für Kunst und Gewerbe of Hamburg (https://sammlungonline.mkg-hamburg.de/de/object/Apotheker-Henkeltopf-/P2017.3.1903a/mkg-e00161237?s=apotheke&h=0). Between 1585 and 1605, the ledgers of the pharmacy show various other payments made in order to purchase additional glass-ceramic containers. On August 4th, 1587, an order to expand the Pharmacy was issued (Canetta 1884). The most significant change happened at the beginning of the XVII century, when it was possible to expand the hospital building, due to an inheritance. In 1640, various construction works are documented, as well as the designation of an area that would become the *Hortum simplicium* (Garden of Simples). The archaeological and palynological analyses carried out in this area have shown a correlation with the plants listed in the archive inventories (Bosi *et al.* 2012, Bottoni *et al.* 2021). Between 1640 and 1643, 575 jars were commissioned by the Pharmacy to the ceramist Michele Valle from Lodi: 37 of these are still preserved in the Hospital collection (Zanchi 1988). New supplies of maiolica jars were secured between 1702 and 1766. These deals were documented in payment records to Carlo and Giovanni Ciano, and to Giuseppe Cadamosti, most likely business intermediaries active in the territory of Lodi. Of these last supplies only 111 survived to this day (Zanchi 1988). The jar ('*albarello*') object of the study presented herein is part of these 111. In order to complete the collection preserved at the Ospedale Maggiore, it is necessary to cite the last 2 jars: a XVII century *albarello* of unknown origin (it does not display the symbol of the Hospital) and a XVIII century jar produced in Bassano (VI, Veneto, Italy).

Scientific studies conducted on the jars

The importance of these artifacts can be found not only in the historical and artistic research proposed here, but also in the study of the jars contents themselves. In fact, this opens several avenues of research linked to the procurement of plant species, their cultivation at the Garden of Simples of the Hospital (Bottoni *et al.* 2021), and to the various mixtures of said species in relation to specific therapeutic uses. The investigation on the 150 jars that survived until today has been recently completed. Particular attention was paid to the type and origin of the remedies that were once preserved in the collection, since these remedies were indicated by inscriptions on the jars themselves (Bottoni *et al.* 2021). As a matter of fact, this investigation stemmed from a careful analysis of the inscriptions with the objective of listing the plant species used in the preparation of the remedies. The same list was used, at a later stage, to identify species that were potentially cultivated in the Garden of Simples of the Hospital during the XVII-XVIII centuries. In order to obtain this information, extensive historical bibliographic research was performed by consulting pharmacopoeias and medicine almanacs from the XV-XIX centuries. The goal of this research was to obtain the recipes of the remedies inscribed on the jars, and thus the plant-based ingredients contained therein. From this work, it was determined that out of the 150 jars, 108 contained remedies which were predominantly plant-based in origin (Bottoni *et al.* 2021). The subsequent tabulation of the jars and all the information thus far gathered allowed for general evaluations concerning the most representative botanical families and genera (Apiaceae and Lamiaceae for the former, with 16 taxa each, and *Mentha*, *Origanum*, and *Prunus* for the latter, with 3 species each). From the historical research it was also possible to determine that the most common ailment treated with the remedies was gastrointestinal distress (n. 46 jars), followed by general state (anti-inflammatory and antipyretics; n. 30), and airways disorders (n. 28). The main objective of the work presented herein was therefore to thoroughly analyze the remedy that was once preserved in jar number 9 of the aforementioned collection. Known as *Electuarium Diacurcumae* (literally turmeric-based electuary), it was used among other things for the treatment of upper airways disorders. By using the study described above as a starting point, the ingredients of the *Electuarium* were investigated pharmacologically and phytochemically.

Materials and Methods

Historical Research

The historical survey led to the identification of the remedy's ingredients once contained in the jar. The inscription on the jar was first analyzed and interpreted with the aid of an ancient antidotary published in 1667 (Collegio dei medici (Roma) *et al.* 1664). All the plant-based ingredients were then tabulated along with the following information: weight, current scientific name (consulting the website www.theplantlist.org and the updated version www.flora.org last accessed on 7th August 2022), botanical family, and used plant parts.

Pharmacological and Phytochemical Research

A pharmacological and phytochemical bibliographic research was carried out on the plant species that were obtained during the historical survey phase. This was done in order to either validate or refute their ancient medicinal uses. To achieve this, interpreting the historical medical terminology of the pathologies in a modern setting became necessary. Several databases were then consulted, such as PubMed, Scopus, Google Scholar, and the bibliographic research online tool known as J.A.N.E. A two-step approach was used during the inquiry. Firstly, either the scientific or the common English name of the species was matched with specific keywords related to respiratory tract disorders (*i.e., Acorus calamus*, 'respiratory disease' or 'airways disorders'). Secondly, the plant name was matched with the specific pathology or activity (*i.e., Acorus calamus*, 'asthma' or 'anti-inflammatory'). Without applying any year filters, the research was primarily focused on systematic reviews and meta-analysis, whenever possible. In all those cases in which both systematic reviews and meta-analyses were unavailable, *in vitro* and *in vivo* studies, as well as clinical trials, were consulted. If possible, the literature inquiry was extended to the mechanism of action. All data was tabulated along with the following information: family, species (scientific), part of the plant historically used, results of the pharmacological and phytochemical research, mechanism of action, and bibliographic references.

Results and Discussion

Jar number 9 - *Electuarium Diacurcumae*

In the book "*Antidotario romano latino, e volgare*" (Roman Latin and vulgar antidotary) (Collegio dei medici (Roma) *et al.* 1664), "*Electuarium Diacurcumae*" (Vase number 9) is described as an effective remedy for the treatment of gastrointestinal and airways problems, as well as increasing body temperature and improving skin complexion. The antidotary outlines the remedy as a mixture of the following plant species: *Cyperus esculentus* L., *Rheum officinale* Baill., *Valeriana officinalis* L., *Lavandula dentata* L., *Crocus* spp, *Daucus carota* L., *Pimpinella anisum* L., *Papaver somniferum* L., *Teucrium scordium* L., *Asplenium ceterach* L., *Glycyrrhiza glabra* L., *Commiphora gileadensis* (L.) C. Chr., *Commiphora myrrha* Engl., *Artemisia absinthium* L., *Eupatorium cannabinum* L., *Rubia tinctorum* L., *Acorus calamus* L., and *Cinnamomum verum* J. Presl. For more information, see Table 1. It is important to highlight that, although the name of the remedy would suggest the presence of *Curcuma longa* L. in the mixture, this plant has not been considered among the ingredients at least since the XVII century. However, considering that a remedy was usually named after the most prominent or important ingredient, it is safe to hypothesize that *C. longa* could have been at one point one of the elements of the electuary's original recipe.

Table 1. Plant-based ingredients of the *Electuarium diacurcumae*, with quantities in decreasing order, and plant parts described in the *Antidotario romano latino, e volgare* (1664).

Quantity	Species	Family	Part of the plant
2 ounces	*Glycyrrhiza glabra* L.	Fabaceae	Syrup (?)
2 ounces	*Asplenium ceterach* L.	Aspleniaceae	Blades
2 ounces	*Teucrium scordium* L.	Lamiaceae	Aerial parts
1 ounce	*Acorus calamus* L.	Araceae	Hypogeal organs
1 ounce	*Cinnamomum verum* J. Presl	Lauraceae	Trunk wood (without rhytidome)
6 drachms	*Cyperus esculentus* L.	Cyperaceae	Hypogeal organs
6 drachms	*Lavandula dentata* L.	Lamiaceae	Flowers/Inflorescences/Parts of the flower
6 drachms	*Rheum officinale* Baill.	Polygonaceae	Hypogeal organs
6 drachms	*Valeriana officinalis* L.	Valerianaceae	Flowers/Inflorescences/Parts of the flower
4 drachms	*Crocus* spp.	Iridaceae	Flowers/Inflorescences/Parts of the flower
4 drachms	*Daucus carota* L.	Appiaceae	Seeds
4 drachms	*Papaver somniferum* L.	Papaveraceae	Seeds
4 drachms	*Pimpinella anisum* L.	Appiaceae	Fruits
2 drachms	*Artemisia absinthium* L.	Asteraceae	Condensed syrup of aerial parts (?)
2 drachms	*Commiphora gileadensis* (L.) C. Chr.	Burseraceae	Fruits, Balm of
2 drachms	*Commiphora myrrha* Engl.	Burseraceae	Gum resin
2 drachms	*Eupatorium cannabinum* L.	Asteraceae	Syrup of aerial parts (?)
2 drachms	*Rubia tinctorum* L.	Rubiaceae	Hypogeal organs

Pharmacological research

In terms of modern physiopathology and pharmacology, the directions given in the text can be applied to a great range of gastrointestinal and respiratory diseases. Furthermore, the mixture can be thought of as having thermoregulator and revulsive activities. Specifically, it is described in the historical source also as a remedy useful to treat 'the swelling that causes heavy breath' ('*il gonfiore per il fiato grosso*') (Collegio dei medici (Roma) *et al.* 1664). We can hypothesize that it could be used in case of asthma and shortness of breath. Regarding respiratory tract diseases, scientific literature ascribes anti-inflammatory, antioxidant, antimicrobial, antiviral, myorelaxant, antitussive, antifibrotic, and anti-asthmatic properties to most of the species of the *Electuarium* (Bottoni *et al.* 2021). In this respect, *Cyperus esculentus* L., *Valeriana officinalis* L., *Daucus carota* L., *Papaver somniferum* L., *Teucrium scordium* L., *Asplenium ceterach* L., *Rubia tinctorum* L., and *Acorus calamus* L. are an exception, for no studies on these activities have been found. For further information, please see Table 2.

***Artemisia absinthium* L.**

In traditional medicine, *Artemisia absinthium* L. was always considered to be interesting in both botany and pharmaceutical science. Among the several properties that this plant is reported to have, a few are related to upper airways pathologies. These activities include antibacterial, anti-inflammatory, antioxidant, antipyretic, and immunomodulant (Ahmad *et al.* 2019, Batiha *et al.* 2020, Danilets *et al.* 2010). The radical scavenging and oxidative stress protection activities should be attributed to the content of phenolic compounds and flavonoids (Kordali *et al.* 2005). The phenolic compounds include gallic, coumaric, vanillic, syringic, salicylic, and chlorogenic acids. The flavonoids, instead, comprise rutin and quercetin. The polysaccharides are most likely responsible for the immunomodulant effect, which is expressed through the regulation of the activation of Th1 cells (Danilets *et al.* 2010). The anti-inflammatory properties of the derivatives of this species are probably the result of the action of flavonoids and sesquiterpenes (Hadi *et al.* 2014). These should inhibit pro-inflammatory factors, such as bradykinins, histamine, prostaglandins, and serotonin. In addition, methanolic extracts are reported to improve the inflammation caused by snake venom (Nalbantsoy *et al.* 2013). Furthermore, several studies have demonstrated a wide-spectrum antibacterial activity towards bacteria of the genera *Staphylococcus*, *Streptococcus*, *Bacillus*, *Salmonella*, and *Pseudomonas*, to name a few (Batiha *et al*, 2020). This effect should be attributed to the essential oils of the species or, more specifically, to the synergy of action between the minor (α-pinene, β-pinene) and the major (camphor, *p*-cymene, caryophyllene) compounds. Several mechanisms of action should be activated in the bacterial cell: interference with membrane fluidity and suppression of proteins, RNA, DNA, and polysaccharides biosynthesis.

Table 2. Pharmacological activities related to the upper airways of the plant-based ingredients of the *Electuarium diacurcumae*, described in the *Antidotario romano latino, e volgare* (1664)

Species	Plant part historically used	Pharmacological activity	Bibliographic reference
Apiaceae			
Pimpinella anisum L.	Fruits	Analgesic, anti-inflammatory, antioxidant, muscle relaxant of tracheal chain	(Akhtar *et al.* 2008, Boskabady & Ramazani-Assari 2001, Shojaii & Abdollahi Fard 2012)
Asteraceae			
Artemisia absinthium L.	Condensed syrup of aerial parts (?)	Antibacterial, antioxidant, anti-inflammatory, antipyretic, immunomodulatory effects	(Ahmad *et al.* 2019, Batiha *et al.* 2020, Danilets *et al.* 2010, Hadi *et al.* 2014, Kordali *et al.* 2005, Nalbantsoy *et al.* 2013)
Eupatorium cannabinum L.	Syrup of aerial parts (?)	Anti-inflammatory	(Chen *et al.* 2011, Ennis 2003)
Burseraceae			
Commiphora gileadensis (L.) C. Chr.	Fruits, Balm of	Antibacterial	(Al-Sieni 2014)
Commiphora myrrha Engl.	Gum resin	Antibacterial, anti-inflammatory, antioxidant, respiratory system disorders	(El-Ashmawy *et al.* 2006, El Ashry 2003, Shen *et al.* 2012, Sotoudeth *et al.* 2019)
Fabaceae			
Glycyrrhiza glabra L.	Syrup of hypogeal parts (?)	Antibacterial, antifibrotic, antifungal, anti-inflammatory, antioxidant, antiparasitic, antiviral, cytotoxic	(Arora *et al.* 2011, Batiha *et al.* 2020b, Cinatl *et al.* 2003, Harwansh *et al.* 2011, Jahan *et al.* 2012, Kuang *et al.* 2018, Shin *et al.* 2007, Zhang *et al.* 2017)
Iridaceae			
Crocus spp.	Flowers/Inflorescences/ Parts of the flower	Anti-inflammatory, myorelaxant on tracheal smooth muscle	(Amin *et al.* 2016, Boskabady*et al.* 2010, Bukhari *et al.* 2015, Hosseinzadeh & Ghenaati 2006, Kianmehr & Khazdair 2020, Nemati *et al.* 2008, Neamati & Boskabady 2010)
Lamiaceae			
Lavandula dentata L.	Flowers/Inflorescences/ Parts of the flower	Anti-asthma, anti-inflammatory, antioxidant	(Almohawes & Alruhaimi 2020, Nadeem *et al.* 2008)
Lauraceae			
Cinnamomum verum J.Presl.	Trunk wood (without rhytidome)	Anti-inflammatory	(Csikós *et al.* 2020, Kim *et al.* 2010, Mendes *et al.* 2016)
Polygonaceae			
Rheum officinale Baill.	Hypogeal organs	Anti-inflammatory	(Chen & Wang 2009)

***Cinnamomum verum* J. Presl.**

Concerning *Cinnamomum verum* J. Presl., scientific literature has documented anti-inflammatory properties of its essential oil in airways disorders. Specifically, an *in vivo* study (Csikós *et al.* 2020) has shown the essential oil obtained from the rhytidome of the species to improve inflammatory parameters in LPS-induced acute pneumonia using murine models. LPS, a component of Gram- bacteria walls, causes interstitial pneumonia and acute pulmonary obstruction through the activation of macrophages Toll-like receptors. This leads to the release of inflammation mediators and the activation of neutrophils. The inhalation of the essential oil, which is rich in cinnamaldehyde, should reduce the chronic inflammatory state that develops in these disorders. In addition, both *in vitro* and *in vivo* studies have demonstrated that the anti-inflammatory activity of cinnamaldehyde develops from the inhibition of macrophages IL-β1 and TNFα release (Kim *et al.* 2010, Mendes *et al.* 2016). It is important to note that although the research described above concerns EOs extracted from the rhytidome, historical sources report only the use of the wood without the rhytidome when used in the *Electuarium Diacurcumae*.

***Commiphora* spp.**

According to scientific literature, several species of the genus *Commiphora* have various therapeutic properties, such as: antifungal, antimicrobial, expectorant, and useful in cases of pharyngitis, sinusitis, chronic and asthmatic bronchitis, and even tubercolosis (El Ashry 2003, Shen *et al.* 2012, Sotoudeth *et al.* 2019). As a matter of fact, *Commiphora gileadensis* (L.) C.Chr. has a long history of traditional uses that are well documented in modern scientific literature (Al-Sieni 2014). Specifically, methanolic and aqueous extracts of the species appear to have demonstrated a promising *in vitro* antibacterial activity. This activity has been also evaluated against bacterial strains of the genera *Staphylococcus* and *Streptococcus*, which are pathogenic to humans. The antibacterial effect is most likely due to several chemical classes, such as: polyphenols, terpenes, alkaloids, lectins, and polypeptides. These should act on the bacterial cell through various mechanisms of action. These include enzymatic inhibition, cellular wall complexing, plasmatic membrane destruction, membrane ionic channels formation, and competitive inhibition with bacterial adhesion molecules (Al-Sieni 2014). On the other hand, the antioxidant activity of the ethanolic derivatives of the congeneric species *Commiphora myrrha* Engl. should originate in the protective action performed by polyphenols towards ROS (El-Ashmawy *et al.* 2006, Sotoudeth *et al.* 2019). Even though scientific literature does not report activities that are directly linked to airways pathologies, it is still possible to correlate the documented antibacterial effect with the historical use of fruit and balm of *C. gileadensis* in treating these disorders. This is also applicable to the antioxidant activity of *C. myrrha*s gum resin.

***Crocus* spp.**

Concerning *Crocus* spp., a recent review has highlighted the potential therapeutic effects of *Crocus sativus* L. in regard to airways illnesses, especially the anti-inflammatory and myorelaxant actions of the flavonoids found in the pistils and petals of the plant (Kianmehr & Khazdair 2020). Both *in vitro* and *in vivo* tests have demonstrated that saffron pistils and kaempferol (extracted from the petals) perform two main actions. First, they significantly diminish lymphocytes and other immune cells' vitality and infiltration in the pulmonary tissue (Bukhari *et al.* 2015). Secondly, they inhibit both the secretion of pro-inflammatory factors such as IFN-γ, interleukins, cytokines, as well as NO levels (Amin *et al.* 2016, Bukhari *et al.* 2015). This, in turn, reduces plasma levels of inflammation mediators, thus protecting the bronchial epithelium from apoptotic events. Furthermore, ethanolic and hydroalcoholic extracts of the species should develop a myorelaxant action on the airway smooth muscle fibers, thereby creating an antitussive effect (Hosseinzadeh & Ghenaati 2006, Kianmehr & Khazdair 2020). As a matter of fact, these types of extracts have been shown to have an agonist action at the β2 adrenergic receptors level (Nemati *et al.* 2008). They also have an antagonist effect on the muscarinic receptors of the bronchial smooth muscle and inhibit the H1 histamine receptors (Boskabady*et al.* 2010, Kianmehr & Khazdair 2020, Neamati & Boskabady 2010). It is worth mentioning that scientific literature documents a myorelaxant action in flavonoids, especially kaempferol (Kianmehr & Khazdair 2020). This effect would then be combined with the other effects described above.

***Eupatorium cannabinum* L.**

In vitro studies have demonstrated that compounds isolated from aerial parts of *Eupatorium cannabinum* L. should modulate the neutrophil-mediated pro-inflammatory response, by controlling the release of the superoxide anion (O_2^-) and by inhibiting elastase release from the neutrophils themselves (Chen *et al.* 2011). Neutrophils have a pivotal role in defending the organism from pathogenic microorganisms, as well as in the etiopathogenesis of various inflammatory-based airways diseases, such as asthma and chronic obstructive pulmonary disease (COPD) (Chen *et al.* 2011, Ennis 2003). When activated, neutrophils secrete pro-inflammatory factors, such as cytokines, ROS, protease, and elastase. These factors contribute to create a state of chronic inflammation that leads to the destruction of the pulmonary parenchyma and to fibrotic events. Therefore, the suppression of the inappropriate or prolonged neutrophil activation can be considered a viable strategy helpful in controlling the inflammatory state in the aforementioned diseases, thus improving symptomatology and progression of the illness as a whole.

***Glycyrrhiza glabra* L.**

In literature, *Glycyrrhiza glabra* L. is described as having multiple biological activities, such as: antibacterial, antifibrotic, antifungal, anti-inflammatory, antioxidant, antiparasitic, antiviral, and cytotoxic (Batiha *et al.* 2020b, Zhang *et al.* 2017). Specifically, the anti-inflammatory and antioxidant activities are particularly relevant in the respiratory diseases. The first occurs by phospholipase A2 inhibition; the second, by blocking ROS release in the neutrophils that are mobilized to the inflammation site (Batiha *et al.* 2020b, Harwansh *et al.* 2011). Furthermore, *in vitro* studies have shown that powder and extracts of the species have antitussive and expectorant properties (Batiha *et al.* 2020b, Jahan *et al.* 2012; Kuang *et al.* 2018). Its efficacy in treating cough, phlegm, and sore throat should be attributed to glycyrrhizin, which helps to decongest the upper airways by favoring expectoration. Additional *in vitro* studies tested both the antibacterial and the antiviral properties of the plant (Batiha *et al.* 2020b). Positive results were obtained with influenza viruses and coronaviruses (SARS) (Cinatl *et al.* 2003). The immunomodulant activity of glycyrrhizic acid was also observed and it was accomplished by preventing viral multiplication and by deactivating the viral particles (Arora *et al.* 2011). Antiviral actions towards influenza-like syndromes were also recorded in *in vivo* studies, as well as anti-inflammatory and antioxidant actions, along with effects in case of allergic reactions and asthma. These effects are mainly obtained from the inhibition of IgE by glycyrrhizin, liquiritigenin, and 18-β-glycyrrhetinic acid (Shin *et al.* 2007). Lastly, clinical trials have demonstrated the antiviral potential of glycyrrhizin accomplished by reducing viral reproduction to such a degree as to approach prophylaxis (Batiha *et al.* 2020b). The glycyrrhizic acid has a very specific action as well. It seems to be the primary bioactive component responsible for a protective action in cases of pulmonary fibrosis (Zhang *et al.* 2017). This disease is characterized by a protracted inflammatory state, oxidative stress, and a progressive deposit of collagen fibers. All of these, in turn, bring about the destruction of the pulmonary tissue and its normal physiology (Zhang *et al.* 2017). In such a situation, *G. glabra*, working in synergy with other species, would produce a protective effect by inhibiting the inflammatory state and improving the pro-fibrotic parameters. In order to accomplish this, the action should occur by modulating the TGF-β1/Smad2 pathway. TGF-β1 represents one of the main mediators of the fibrotic process through the phosphorilation of the Smad proteins. When this happens, they are able to recall cytokines and pro-inflammatory mediators to the site of action. Furthermore, the species seems to inhibit the overexpression of the NOX4 enzymatic isoform during the fibrotic process. This would imply a significant improvement of the oxidative stress, which is one of the root causes of pulmonary fibrosis (Zhang *et al.* 2017).

***Lavandula dentata* L.**

Scientific literature presents a few *in vivo* studies that document the antioxidant and anti-inflammatory properties of *Lavandula dentata* L., useful in treating asthma-like conditions (Almohawes & Alruhaimi 2020). As a matter of fact, inflammation and oxidative stress are among the factors at the root of asthma (Nadeem *et al.* 2008). The activities of lymphocytes, macrophages, and other immune system cells cause an increase of reactive oxygen species (ROS). These, in turn, contribute to the beginning and development of the airways inflammatory state, as well as alter endogenous antioxidant systems (superoxide dismutase, catalase, and glutathione peroxidase). In animal models (Almohawes & Alruhaimi 2020), extracts of *L. dentata* have shown a heavy antioxidant effect, especially in allergic asthma cases, thus alleviating asthma attacks and improving the organism's natural defences. In fact, these extracts should reduce levels of IgE freed through the activation of T-helper cells in cases of allergic response. They would also lead to the reduction of malondialdehyde (MDA), which is the final product of lipidic peroxidation and is one of the causes of the inflammation. Such synergic activities could then improve the oxidative and inflammatory states that underlie the asthmatic symptoms.

***Pimpinella anisum* L.**

According to scientific literature, *Pimpinella anisum* L. and its derivatives have biological activities on several organ systems, including the respiratory one (Shojaii & Abdollahi Fard 2012). Among these activities, it is possible to identify a direct myorelaxant action on the bronchial smooth muscle and a subsequent bronchodilator effect of aqueous and ethanolic extracts and of the essential oil obtained from the seeds (Boskabady & Ramazani-Assari 2001). Furthermore, the essential oil performs analgesic, anti-inflammatory, and antioxidant actions that could be useful in treating airways pathologies. The plant has well documented antibacterial properties against strains potentially involved in airways diseases, such as *Staphylococcus aureus*, *Klebsiella pneumoniae* and bacteria of the genus *Streptococcus*. *P. anisum* also performs antiviral and immunomodulant activities (Akhtar *et al.* 2008; Shojaii & Abdollahi Fard 2012). However, it is important to note that several of the activities described above are the result of synergic effects between *P. anisum* and derivatives of other species.

Rheum officinale **Baill.**

Literature data for *Rheum officinale* Baill. describes an anti-inflammatory activity on the lungs in case of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) (Chen & Wang 2009). *In vivo* studies have shown that the plant halts the rise of the phlogistic state along the gut-liver-lung axis, which in turn is implicated in the pathologies outlined above. Specifically in the lungs, this species should develop an anti-inflammatory action by reducing the pulmonary capillary permeability to pro-inflammatory factors. It also reduces NO and TNF-α levels and inhibits myeloperoxidase and phospholipase A2 enzyme activities (Chen & Wang 2009).

Curcuma longa **L.**

Although *C. longa* was not among the ingredients of the XVII century recipe, it can be possible that this plant was in fact part of the original recipe, thus giving the remedy its name. For this reason, we extended the bibliographic research to this species and its secondary metabolites potentially active on the respiratory tract. The curcuminoids in the plant represent a group of secondary metabolites responsible for a variety of biological activities, which were evaluated in *in vitro*, *ex vivo*, and *in vivo* studies, as well as in clinical trials. Specifically, curcumin oral supplements administered to healthy children with recurrent airway infections could lead to a positive modulation of the T Cell-mediated immune response (Salehi *et al.* 2018, Zuccotti *et al.* 2009). Furthermore, both *in vitro* and *in vivo* studies ascribe anti-inflammatory, antioxidant, and anti-fibrotic properties to curcumin (Lelli *et al.* 2017). These properties could be beneficial in treating a variety of pulmonary pathologies that are characterized by an abnormal inflammatory response, such as asthma, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome, and pulmonary fibrosis. Curcumin's anti-inflammatory activity is most likely expressed through the regulation of transcription factors and the release of cytokines, adhesion molecules, and enzymes (Lelli *et al.* 2017). Specifically, the inhibition of the NF-kB nuclear transcription factor should reduce the COX-2 and 5-LOX expression, thus reducing the synthesis of prostaglandins. An additional mechanism of action could reduce the levels of pro-inflammatory interleukins such as IL-5 and IL-8, which are chemotactic factors released by monocytes, macrophages, and activated T-cells. Lastly, curcumin inhibits the proliferation of T-helper lymphocytes leading to a reduction of IgG levels (Lelli *et al.* 2017, Sharma *et al.* 2007). Furthermore, it lowers histamine release by mastocytes and down-regulates macrophages and neutrophiles (Douglas 1993). All these factors contribute to a reduced inflammatory state. Therefore, in chronic inflammation cases, this anti-inflammatory activity could prevent fibrotic events in the pulmonary parenchyma. Complementary to this action is the antioxidant effect which has been observed in both *in vitro* and *in vivo* studies performed on the molecule (Lelli *et al.* 2017, Salehi *et al.* 2019). Curcumin should achieve a radical scavenging effect by keeping antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase in an active state. Curcumin can inhibit iNOS activity as well (Lelli *et al.* 2017, Menon *et al.* 2007). This should lower the expression of NO-mediated inflammatory events. All the mechanisms described above support the potential inclusion of the hypogeal parts and leaves of *C. longa* in the original recipe of *Electuarium Diacurcumae*.

Conclusions

Extraordinary public and private collections of ancient pharmacy maiolica jars can still be admired around the world nowadays. These jars are considered an invaluable historical-artistic source of knowledge concerning the ancient use of medicinal plants. The investigation presented in this work is part of a wider project, which had the main purpose of underline the importance of the XVII-XVIII century collection preserved in the Pharmacy annexed to the Ospedale Ca' Granda in Milan. Through a multidisciplinary approach, it was possible to study the contents of one of the 150 majolica jars of the collection from a pharmacological and phytochemical point of view. The remedy once contained in jar number 9, known as *Electuarium Diacurcumae*, was a concoction useful to treat several pathologies, such as upper airways disorders and included 18 plant-based ingredients. Through the mechanisms of actions clarified by the modern scientific literature consulted, our investigation revealed that at least 9 ingredients out of the 18 of the electuary would have effectively brought benefit in the treatment of several inflammation-based airways disorders, infections, and asthma mainly due to their antioxidant, anti-inflammatory, and antibacterial properties. Therefore, this study lays the groundwork for a wider and thorough investigation that could potentially involve each maiolica jar of the collection and the historical medicinal use of the remedies once contained therein. This would corroborate both the incredible historical value of the collection and the scientific relevance of its ancient contents.

Declarations

List of abbreviations: Th1, T helper cell type 1; RNA, Ribonucleic acid; DNA, Deoxyribonucleic acid; LPS, Lipopolysaccharide; TNF-α, Tumor necrosis factor-α; ROS, Reactive oxygen species; IFN-γ, Interferon gamma; NO, Nitric oxide; IgE, Immunoglobulin E; TGF-β1, Tumor growth factor β1; Smad2 proteins, Small Mothers Against Decapentaplegic 2 proteins; NOX4, NADPH Oxidase 4; NF-κB, Nuclear factor-kappa B; COX-2, Cyclooxygenase-2; 5-LOX, 5-lipoxygenase; IL-5, Interleukin-5; IL-8, Interleukin-8; IgG, Immunoglobulin G; iNOS, Inducible nitric oxide synthase.

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