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Italian folk plant-based remedies to heal headache (XIX-XX century)

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ABSTRACT

Background: Headache has been recognized since antiquity. From the late nineteenth to the early to mid-twentieth century, Italian folk remedies to treat headache were documented in a vast *corpus* of literature sources.
Aim: The purpose of this paper is to bring to light the plant-based treatments utilized by Italian folk medicine to heal headache in an attempt to discuss these remedies from a modern pharmacological point of view. Moreover, we compare the medical applications described by Hippocrates, Pliny the Elder, Dioscorides, Galen and Serenus Sammonicus with those utilized by Italian folk medicine to check if they result from a sort of continuity of use by over two thousand years.
Results: A detailed search of the scientific data banks such as Medline and Scopus was undertaken to uncover recent results concerning the anti-inflammatory, anti-nociceptive and analgesic activities of the plants. Fifty-eight (78.4%) plant-based remedies have shown *in vivo, in vitro* or in human trials a large spectrum of anti-inflammatory, anti-nociceptive and analgesic activities.

Moreover, thirty-one of remedies (41.9%) were already included in the pharmacopoeia between the 5th century BC and the 2nd century AD.
Conclusion: Italian folk medicine could be a promising source of knowledge and could provide evidences for active principles that have not as of yet been fully used for their potential.

1. Introduction

The third edition of the International Headache Society classifies headache into “primary” and “secondary” disorders. The primary headaches, representing 90% of all cephalalgias, include migraine, tension-type headache, cluster headache, trigeminal autonomic cephalalgias, and other primary headaches (such as cold-stimulus headache, external-pressure headache, etc). The secondary ones are caused by an underlying disease, such as head injuries, infections, vascular disorders or tumors (HIS, 2013). The World Health Organization claims that, nowadays, headache is among the most prevalent disorders in the world (WHO, 2011), but it is reasonable to state headache has existed as long as humankind (Magiorkinis et al., 2009).

In fact, in the opinion of several researchers, early medical treatments to relieve headache suffers were cranial trepanations performed by Neolithic populations (around 9000 BCE). The practice of removing pieces of bone from skull of a living individual was connected with the belief to release the evil spirits inhabited in the head of the patients (Campillo, 1984). The idea that the cause of headache, as other ailments, could be ascribable to an attack of divine or supernatural forces, was common during antiquity. The first written descriptions of headache symptoms were found in Mesopotamian tablets (4000 BCE) in which the attack was attributed to an evil called *Tíu*. The pain was cured with an exorcism using an ointment of human bone reduced to ashes and mixed with cedar oil or applying other unpleasant substances (Green et al., 2005).

Later, ancient Egyptian medical papyri, such as the Ebers papyrus (1550 BCE) contained remedies and prescriptions corresponding to therapeutic remedies which ranged from supernatural to natural, from magical to empirical (Karenberg and Leitz, 2001).

The beginning of a rational approach arises from Greek medicine: Hippocrates of Kos (460-377 BCE) argued that disease is a general phenomenon of organism without supernatural interventions. He suggested headache occurred when black bile, yellow bile, blood and phlegm were out of harmony in the body, so he treated head pain with bloodletting or applying herbs to the head to drain excess liquids. Hippocrates was, also, the first to describe a migraine with aura (Green et al., 2005).

Abbreviation: NSAIDs, Nonsteroidal anti-inflammatory drugs; NF-κB, Nuclear Factor-κB; COX-2, Cyclooxygenase-2; PGE-2, Prostaglandin E-2; TNF-α, Tumor Necrosis Factor-α; NO, Nitric Oxide; IL-1, Interleukin-1; IL-8, Interleukin-8; LPS, lipopolysaccharide; MAO-A, Monoamino Oxidase-A; 5-HT, 5-hydroxytriptamine; NE, Norepinephrine

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In the Roman period, Pliny the Elder (23–79 CE) who was not a physician but a writer, in his *Naturalis Historia*, cites about one hundred remedies taken from animal (man included) and vegetable kingdoms. He subdivides headaches into five categories, based on the symptoms: 1) pain of entire head; 2) pain localized to the temples; 3) pain to the nape; 4) pain accompanied by sense of warmth and, lastly, 5) chronic headache. The contemporaries Aulus Cornelius Celsus (c.25 BCE-c.50 CE) and Areteus the Cappadocian (1st century AD) recommend, as therapeutic remedies, bloodletting, diet, application of warm or cold water and cauterization. Later, Galen (129–199 CE) was the first to introduce the term *hemicrania* (Zanchin, 2010).

The purpose of this paper is to bring to light the plant-based treatments utilized by Italian folk medicine for headache, between the late nineteenth century and the early to mid-twentieth century, to "rediscover" remedies that nowadays are mostly no longer used. For this reason, a systematic review of literature sources was carried out to investigate practices, performed by Italian folk medicine to heal headache during the above mentioned period, in the light of the current scientific knowledge.

The starting point of this period stands for the time in which the study of folk traditions as folk treatments to heal several diseases, arose and spread out with an appropriate methodology (Cirese, 1996). On the other hand, the end of the 1950's represents the period in which the countryside was massively abandoned so that, for the first time in Italy, more people were employed in industry than in agriculture (ISTAT, 2011). This event played an important role in the so called "economic boom" and in the social and cultural change of Italy which was transformed from a mainly rural to a modern country (Sapelli, 1991).

Moreover, in this paper we compare medical applications described by Hippocrates, Pliny the Elder, Dioscorides, Galen and Serenus Sammonicus to verify possible similarities with Italian folk remedies to treat headache.

2. Materials and methods

The National Library Service website of the Italian Libraries Network was consulted to find the literature sources. For this purpose, the following key words were entered: "folk medicine", "usages and customs", "folk traditions", "traditional knowledge", and "folk remedies". This approach allowed us to unearth about one hundred sources (books and journal articles), written by anthropologists, physicians, ethnographers, folklorists, and scholars of local history.

Among these sources, twenty-seven showed at least one plant-based treatment to heal headache. The plants have been identified as species in two cases: 1) when they were described by their scientific name; 2) when they are mentioned by their Italian name. In the last case, the plant (e.g. onion) has been referred to species (e.g. *Allium cepa* L.) only when there was no doubt. In all other cases, only the genus was attributed (e.g. incense, *Boswellia* spp.).

The names of the plant families were reported according to the guidelines of Angiosperm Phylogeny Group (Stevens, 2001).

Despite new discoveries accumulated over the last 30 years have increased the current knowledge, etiopathogenetic mechanisms of the headache remain unclear and the most common therapeutic approaches are based on analgesic or NSAIDs administration (SISC, 2011). For these reasons, a detailed search of the scientific data banks such as Medline and Scopus was undertaken to uncover recent results concerning the anti-inflammatory, anti-nociceptive, and analgesic activities for each plant-based treatment.

Finally, the collected data were compared with plant-based remedies described in the *Corpus Hippocraticum* (a collection of 62 medical works written between the 5th century BCE and the 2nd century AD that were ascribed to Hippocrates), *Naturalis Historia* (Pliny the Elder, 1st century AD), *De Materia Medica* (Dioscorides, 1st century AD), *Opera Omnia* (Galen, 2nd century AD) and *Liber Medicinalis* (Serenus Sammonicus, 2nd century AD).

3. Results

In the texts of Italian folk medicine, consulted in this work, we have not found different terms to denote different types of cephalalgia. The pain was described generically with the term "headache" or "migraine", used as synonym. Even if, only in few cases, the consultation of the sources has highlighted types of headache that affects temple, forehead and sometimes extends to the periorbital region. More details, instead, have been claimed about aetiology. Italian folk healers observed that headache could be related to environmental, biological or magical events. Headache was known to be associated to arthritis, cold, blood circulation disorders, oversleeping, fasting and, on the contrary, eating heartily. The exposure to sun, heat, cold and draught as well as sleeping in a field of spring crocus (*Crocus albiflorus* Kit. ex Schult.), meadow saffron (*Colchicum autumnale* L.) and common laburnum (*Laburnum anagyroides* Medik.) was thought to cause headache attacks. Moreover, Italian folk healers believed that magical factors including evil eye, sleeping under the moon or under a walnut tree, watching a toad and combing one's hair at Friday, could induce headache.

The collected data pointed out 74 plants utilized by Italian folk medicine to heal headache belonging to 39 families. Out of these, the most cited were Asteraceae (16.2%) and Lamiaceae (13.5%). This study has highlighted 76 plant-based remedies which were taken through the following routes of administrations: topical (59.2%), oral (27.6%), and inhalation (13.2%). Oral administration was performed swallowing decoctions (38.1), infusions (28.6%), crude plant parts (23.8%), and alcoholic extracts (9.5%). Inhalation was performed breathing steams (50%), sniffing powder (30%), and aspirating juice (20%). The parts of plants used are the following: leaves (27.8%), aerial parts (26.6%), flowers (16.5%), fruits (13.9%), seeds (8.9%), roots (2.5%), tubers (2.5%) and resins (1.3%) (Table 1).

The historical sources consulted in this paper highlighted that, among the 74 plants utilized by Italian folk medicine between the late nineteenth and the early to mid-twentieth century for the treatment of headache, 31 (41.9%) were already included in the pharmacopoeia between the 5th century BCE and the 2nd century AD (Table 1).

Nowadays, a significant percentage (78.4%, N = 58) of plants utilized by Italian folk medicine showed, *in vivo, in vitro* or in human trials, an analgesic, anti-nociceptive and anti-inflammatory properties which could explain and justify their potential role in the cure of headache. In Table 2 these pharmacological activities are summarized.

4. Discussion

Natural products contribute significantly to discover new bioactive compounds for development of drugs to treat human diseases. More than half of all approved small-molecule drugs, in fact, show a structure originally ascribable to natural products. In addition, a large number of natural products, nowadays, are used in clinical trials (Stratton et al., 2015).

Similarly, natural treatments, derived from plants and animals, have been an unlimited "reservoir" of remedies since ancient times, and their use has been transmitted for centuries in traditional medicine (Confessor et al., 2009). According to De Vos (2010), natural remedies of the ancient Mediterranean area had a noteworthy lifespan in the European *materia medica*, well established until the 19th century.

In this work, 41.9% of the plant-based treatments utilized by Italian folk medicine between the late nineteenth and the early to mid-twentieth century to heal headache seems to represent the continuity of the medical tradition over about two thousand years.

Several recent studies have shown that knowledge of folk medicine is based upon the pharmacopeia of ancient Greece and Rome (Pollio et al., 2008; Leonti et al., 2009; Tagarelli et al., 2010, 2013), even if the biggest obstacle is represented by the impossibility to state with certainty which plants (and diseases) are which. These difficulties are not insurmountable. An interdisciplinary approach with philological,

Table 1
Plants used by Italian folk medicine to treat headache and mentioned to serve the same purpose, by historical sources (5th century BCE–2nd century AD).

Family/scientific/common name	Italian name	Plant parts	Route of administration	References	Historical sources	References
Adoxaceae						
***Sambucus nigra* L. (Elderberry)**	**Sambuco**	Fr, Lf	Use suffumigations of elderberry flowers boiled in the water; Smear on the temples elderberry leaves	Ostermann (1894); Nardi (1935))	Hippocrates (*De Morbis II, 19*).	(Potter, 1988a)
Amarantaceae						
***Beta vulgaris* L. (Red beet)**	**Bieta**	Ap	Aspirate by nose a juice mixture obtained pressing the following plants: anemone, red beet, cabbage, greater celandine, cyclamen, and onion	(Pignatari, 1894)	Hippocrates (*De Morbis II, 12; De Affectionibus Interioribus 48*). Pliny (*Naturalis Historia XX, 27*). Dioscorides (*De Materia Medica II, 149*).	(Potter, 1988a, 1988b) (Plinio, 1985) (Kühn, 1829)
Amaryllidaceae						
***Allium cepa* L. (Onion)**	**Cipolla**	Ft	Aspirate by nose a juice mixture obtained pressing the following plants: anemone, red beet, cabbage, greater celandine, cyclamen, and onion	(Pignatari, 1894)	Dioscorides (*De Materia Medica II, 180*).	(Kühn, 1829)
Apiaceae						
***Foeniculum vulgare* Mill. (Fennel)**	**Finocchio**	Lf	Put on the head a cloth moistened with infusion of the following plants: wormwood, wild thyme, marjoram, thyme, fennel, rosemary, sage, and costmary	(Coronedi-Berti, 1877)	Galen (*Opera Omnia XII, 568; XIV, 399*).	(Kühn, 1826, 1827)
***Pimpinella anisum* L. (Anise)**	**Anice**	Sd	Inhale powder obtained from a mixture of pyrethrum, white hellebore, betony, anise, and fumitory seeds	(Finamore, 1894)	Pliny (*Naturalis Historia XX, 73*). Dioscorides (*De Materia Medica III, 58*).	(Plinio, 1985) (Kühn, 1829)
Asparagaceae						
Convallaria majalis L. (Wood lily)	Mughetto	Fr	Drink wine infusion of wood lily	(Pedrotti and Bertoldi, 1930)	–	–
Leopoldia comosa (L.) Parl. (Tassel hyacinth)	Cipollaccio	Tb	Smear on the temples bulbs in halves of tassel hyacinth	(Adriano, 1932)	–	–
Asteraceae						
Achillea atrata L. (Black yarrow)	Millefoglio del calcare	Ap	Drink infusion of black yarrow	(Chiovenda-Bensi, 1955)	–	–
***Achillea millefolium* L. (Yarrow)**	**Millefoglio**	Fr	Drink infusion of yarrow combined in equal amounts with chamomile	(Chiovenda-Bensi, 1955)		
Achillea erba-rotta All. subsp. moschata (Wulfen) I. Richardson (Iva)	Millefoglio del granito	Ap	Drink infusion of iva	(Chiovenda-Bensi, 1955)	–	–
***Arctium lappa* L. (Burdock)**	**Bardana maggiore**	Lf	Put on the head fresh leaves of burdock mixed in olive oil	(Pedrotti and Bertoldi, 1930)	–	–
***Arnica montana* L. (Arnica)**	**Arnica**	Fr	Drink spirit in which arnica flowers were soaked	(Chiovenda-Bensi, 1955)		
***Artemisia absinthium* L. (Wormwood)**	**Assenzio**	Lf	Put on the head a cloth moistened with infusion of the following plants: wormwood, wild thyme, marjoram, thyme, fennel, rosemary, sage, and costmary; Drink decoction of wormwood	(Coronedi-Berti, 1877; Ostermann, 1894)	Galen (*Opera Omnia XII, 524*).	(Kühn, 1826)
***Artemisia* spp. (Artemisia)**	**Artemisia**	Ap, Lf	Apply on the forehead a poultice of artemisia and white horehound mixed with vinegar; Drink decoction of artemisia	(Pasquarelli, 1987; Ostermann, 1894)	–	–
***Glebionis coronaria* (L.) Cass. ex Spach (Garland)**	**Crisantemo giallo**	Fr	Put on the head garland flowers	(Pitrè, 1896)	–	–
***Helianthus annus* L. (Sunflower)**	**Girasole**	Sd	Drink Holy Water infusion of sunflower seeds	(Ostermann, 1894)	–	–
***Matricaria chamomilla* L. (Chamomile)**	**Camomilla**	Fr	Drink infusion of chamomile alone or combined in equal amounts with yarrow; Put on the head a poultice of chamomile; Apply two red hosts impregnated with chamomile water, when the pain was localized in the periorbital area	(Chiovenda-Bensi, 1955; Pedrotti and Bertoldi, 1930; Latronico, 1935)	–	–
***Tanacetum balsamita* L. (Costmary)**	**Erba di Santa Maria**	Lf	Put on the head a cloth moistened with infusion of the following plants: wormwood, wild thyme, marjoram, thyme, fennel, rosemary, sage, and costmary	(Coronedi-Berti, 1877)	–	–
Tanacetum cinerariifolium (Trevir.) Sch. Bip. (Pyrethrum)	Piretro	Ap	Inhale powder obtained from a mixture of pyrethrum, white hellebore, betony, anise, and fumitory seeds; Chew stavesacre and pyrethrum	(Finamore, 1894; Pignatari, 1894)	–	–
Brassicaceae						
***Brassica oleracea* L. (Cabbage)**	**Cavolo**	Lf	Put on the head fresh leaves of cabbage mixed in warm oil; Aspirate	(Ostermann, 1894; Pignatari,	Hippocrates (*De Morbis II, 19*).	(Potter, 1988a)

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Table 1 *(continued)*

Family/scientific/common name	Italian name	Plant parts	Route of administration	References	Historical sources	References
			by nose a juice mixture obtained pressing the following plants: anemone, red beet, cabbage, greater celandine, cyclamen, and onion	1894)	Pliny (*Naturalis Historia XX, 33*). Galen (*Opera Omnia XIV, 318, 579*).	(Plinio, 1985) (Kühn, 1827)
Lunaria annua L. (Honesty)	Erba argentina	Ap	Smear on the temples aerial parts of honesty	(De Giacomo, 1896)	–	–
Burseraceae						
***Boswellia* spp. (Incense)**	**Incenso**	Ap	Use suffumigations of incense boiled in the water	(Sembianti, 1936)	–	–
Campanulaceae						
Campanula glomerata L. (Dane's blood)	Campanula a mazzetti	Fr, Lf	Drink decoction of Dane's blood	(Pedrotti and Bertoldi, 1930)	–	–
Cactaceae						
***Opuntia ficus indica* (L.) Mill. (Cactus pear)**	**Fico d'India**	Ft	Smear on the temples sliced fruits of cactus pear	(Zanetti, 1892)	–	–
Cannabaceae						
***Humulus lupulus* L. (Hop)**	**Luppolo**	Fr	Eat hop fruits in barley soup	(Pedrotti and Bertoldi, 1930)	–	–
Caprifoliaceae						
***Valeriana officinalis* L. (Valerian)**	**Valeriana**	Ap, Fr	Wash head with valerian flowers water; Rub on head with valerian flowers; Rub on forehead the whole plant of valerian	(Ostermann, 1894; Ferraro, 1885)	–	–
Crassulaceae						
***Sempervivum tectorum* L. (Common houseleek)**	**Semprevivo dei tetti**	Ap	Put on the head common houseleek	(De Nino, 1891)	Dioscorides (*De Materia Medica IV, 88*). Galen (*Opera Omnia XII, 508*).	(Kühn, 1829) (Kühn, 1826)
Cucurbitaceae						
***Cucumis sativus* L. (Cucumber)**	**Cetriolo**	Ft	Smear on the temples peel of cucumber; Apply on the forehead sliced cucumber	(Adriano, 1932; Lombardi-Satriani, 1970; Marzano, 1890)	Hippocrates (*De Morbis II, 12*).	(Potter, 1988a)
Cucurbita maxima Duchesne (Pumpkin)	Zucca	Ft	Brought pumpkin in halves like a hat	(Pasquarelli, 1987; Lombardi-Satriani, 1970; Marzano, 1890)	Galen (*Opera Omnia XII, 570; XIV, 557*).	(Kühn, 1826, 1827)
***Ecballium elaterium* (L.) A. Rich. (Squirting cucumber)**	**Cocomero asinino**	Ft	Aspirate by nose a juice obtained pressing squirting cucumber fruit	(Pitrè, 1896)	Dioscorides (*De Materia Medica IV, 155*). Galen (*Opera Omnia XIV, 316*).	(Kühn, 1829) (Kühn, 1827)
Cupressaceae						
***Juniperus communis* L. (Juniper)**	**Ginepro**	Ft	Use suffumigations of juniper berries boiled in the water	(Sembianti, 1936)	–	–
Ericaceae						
***Vaccinium myrtillus* L., *Vaccinium vitis idaea* L. (Bilberry)**	**Mirtillo**	Ft	Drink spirit in which bilberry fruits were soaked	(Pedrotti and Bertoldi, 1930)	–	–
Fabaceae						
Vicia faba L. (Broad bean)	Fava	Sd	Smear on the temples seeds in halves of broad bean	(Zanetti, 1892)	Galen (*Opera Omnia XIV, 399, 548*).	(Kühn, 1827)
Gentianaceae						
***Gentiana lutea* L. (Gentian)**	**Gentiana**	Ap	Drink decoction of gentian	(De Nino, 1891)	–	–
Jungladaceae						
***Juglans regia* L. (Walnut)**	**Noce**	Lf	Put on the head fresh leaves of walnut	(Pitrè, 1896)	Pliny (*Naturalis Historia XXIII, 45*). Galen (*Opera Omnia XII, 569*).	(Plinio, 1985) (Kühn, 1826)
Hypericaceae						
***Hypericum hircinum* L. (Stinking tutsan)**	**Ruta caprina**	Ap	Bring on the head a bundle of stinking tutsan	(Geraci, 1957; Pagano, 1992; Lanza, 2006)	–	–
Iridaceae						
***Iris germanica* L. (German iris)**	**Giaggiolo**	Rt	Spread on the head pounded root of German iris	(Pedrotti and Bertoldi, 1930)	Pliny (*Naturalis Historia XXI, 83*). Dioscorides (*De Materia Medica I, 1*). Galen (*Opera Omnia XII 503, 511, 556, 558, 569, 579, 581, 597; XIV, 316*).	(Plinio, 1985) (Kühn, 1829) (Kühn, 1826, 1827)
Lamiaceae						
***Lavandula angustifolia* Mill., *Lavandula stoechas* L. (Lavender)**	**Lavanda**	–	–	(Ostermann, 1894)	–	–

(continued on next page)

Table 1 *(continued)*

Family/scientific/common name	Italian name	Plant parts	Route of administration	References	Historical sources	References
***Marrubium vulgare* L. (White horehound)**	**Marrubio**	Ap	Apply on the forehead a poultice of artemisia and white horehound mixed with vinegar	(Pasquarelli, 1987)		
***Mentha pulegium* L. (Pennyroyal)**	**Puleggio**	Ap	Use suffumigations of pennyroyal boiled in the wine	(Pitrè, 1896)	Pliny (*Naturalis Historia XX, 54*). Galen (*Opera Omnia XII, 524, 568; XIV, 399*). Serenus Sammonicus (*Liber Medicinalis I, 15*).	(Plinio, 1985) (Kühn, 1826, 1827) (Pépin, 1950)
***Origanum majorana* L. (Marjoram)**	**Maggiorana**	Ap, Lf	Put on the head a cloth moistened with infusion of the following plants: wormwood, wild thyme, marjoram, thyme, fennel, rosemary, sage, and costmary; Bring on the head marjoram in a sack; Inhale dried and pulverized leaves of marjoram	(Coronedi-Berti, 1877; Ostermann, 1894; Pitrè, 1896)	Galen (*Opera Omnia XII 503, 511, 512*).	(Kühn, 1826)
***Rosmarinus officinalis* L. (Rosemary)**	**Rosmarino**	Lf	Put on the head a cloth moistened with infusion of the following plants: wormwood, wild thyme, marjoram, thyme, fennel, rosemary, sage, and costmary	(Coronedi-Berti, 1877)	–	–
***Salvia officinalis* L. (Sage)**	**Salvia**	Lf	Put on the head a cloth moistened with infusion of the following plants: wormwood, wild thyme, marjoram, thyme, fennel, rosemary, sage, and costmary; Drink decoction of sage	(Coronedi-Berti, 1877; Chiovenda-Bensi, 1955)	–	–
***Stachys officinalis* (L.) Trevis. (Betony)**	**Betonica**	Ap	Inhale powder obtained from a mixture of pyrethrum, white hellebore, betony, anise, and fumitory seeds; Spread on the head dried and powdered betony mixed with honey; Drink decoction of betony collected during St. John's night	(Finamore, 1894; Pedrotti and Bertoldi, 1930; Zanetti, 1892)	Dioscorides (*De Materia Medica IV, 2*).	(Kühn, 1829)
Teucrium spp.	Camedrio	–	–	(Tancredi, 1938)	–	–
***Thymus serpyllum* L. (Wild thyme)**	**Serpillo**	Lf	Put on the head a cloth moistened with infusion of the following plants: wormwood, wild thyme, marjoram, thyme, fennel, rosemary, sage, and costmary	(Coronedi-Berti, 1877)	Pliny (*Naturalis Historia XX, 90*). Dioscorides (*De Materia Medica III, 40*). Galen (*Opera Omnia XII, 512, 556, 558, 579, 597*)	(Plinio, 1985) (Kühn, 1829) (Kühn, 1826)
***Thymus* spp.**	**Timo**	Lf	Put on the head a cloth moistened with infusion of the following plants: wormwood, wild thyme, marjoram, thyme, fennel, rosemary, sage, and costmary	(Coronedi-Berti, 1877)	–	–
Lauraceae						
***Laurus nobilis* L. (Bay laurel)**	**Alloro**	Lf	Spread forehead with oil extracted from bay laurel	(Nardi, 1935)	Pliny (*Naturalis Historia XXIII, 43, 80*). Galen (*Opera Omnia XII 503, 512, 514, 556, 558, 570, 579, 580, 581, 597*).	(Plinio, 1985) (Kühn, 1826)
Melanthiaceae						
Paris quadrifolia L. (Herb Paris)	Uva di volpe	Lf	Put on the head fresh leaves of herb paris	(Ostermann, 1894)	–	–
***Veratrum album* L. (White hellebore)**	**Elleboro bianco**	Ap	Inhale powder obtained from a mixture of pyrethrum, white hellebore, betony, anise, and fumitory seeds	(Finamore, 1894)	Hippocrates (*De Morbis II, 12*). Pliny (*Naturalis Historia XXV, 89*)	(Potter, 1988a) (Plinio, 1985)
Oleaceae						
***Olea europea* L. (Olive)**	**Olivo**	Ft	Spread head with olive oil	(Bernoni, 1878)	Pliny (*Naturalis Historia XXIII, 34*). Galen (*Opera Omnia XII, 513, 558, 593, 596; XIV, 315, 316, 318*).	(Plinio, 1985) (Kühn, 1826, 1827)
Papaveraceae						
***Chelidonium majus* L. (Greater celandine)**	**Celidonia**	Ap	Aspirate by nose a juice mixture obtained pressing the following plants: anemone, red beet, cabbage, greater celandine, cyclamen, and onion	(Pignatari, 1894)	Serenus Sammonicus (*Liber Medicinalis I, 23*).	(Pépin, 1950)
***Fumaria officinalis* L. (Fumitory)**	**Fumaria**	Ap	Inhale powder obtained from a mixture of pyrethrum, white hellebore, betony, anise, and fumitory seeds	(Finamore, 1894; Ferraro, 1885)	–	–
Pinaceae						
Abies alba Mill. (Silver fir)	Abete	Rs	Smear on the temples silver fir resin	(Pedrotti and Bertoldi, 1930)	–	–
Plantaginaceae						
***Plantago* spp. (Plantain)**	**Piantaggine**	Ap	Smear on the temples plantain pounded in vinegar and mixed with albumen	(Ostermann, 1894)	Galen (*Opera Omnia XII, 508*).	(Kühn, 1826)
Poaceae						
***Avena sativa* L. (Oat)**	**Avena**	Sd	Eat oat seeds put in the water and choosing the floating ones	(Ferraro, 1885)	–	–

(continued on next page)

Table 1 *(continued)*

Family/scientific/common name	Italian name	Plant parts	Route of administration	References	Historical sources	References
***Triticum* spp. (Wheat)**	**Frumento, Grano**	Sd	Smear on the temples wheat flour mixed with vinegar	(Nardi, 1935)	–	–
Portulacaceae						
***Portulaca oleracea* L. (Verdolaga)**	**Portulaca**	Lf	Eat verdolaga salad; Apply both on the temples and forehead leaves of verdolaga	(Coronedi-Berti, 1877; Finamore, 1894)	Pliny (*Naturalis Historia XX, 81*). Dioscorides (*De Materia Medica II, 150*). Galen (*Opera Omnia XII, 508; XIV, 315*)	(Plinio, 1985) (Kühn, 1829) (Kühn, 1826, 1827)
Primulaceae						
***Cyclamen* spp. (Cyclamen)**	**Ciclamino**	Ap, Lf	Put on the head cyclamen mixed with fat and butter; Aspirate by nose a juice mixture obtained pressing the following plants: anemone, red beet, cabbage, greater celandine, cyclamen, and onion	(Ostermann, 1894; Pignatari, 1894)	Pliny (*Naturalis Historia XXV, 84*). Dioscorides (*De Materia Medica II, 193*).	(Plinio, 1985) (Kühn, 1829)
Primula veris L. (Cowslip)	Primula	Ap	Put on the head a hot pack of cowslip	(Pedrotti and Bertoldi, 1930)	–	–
Ranunculaceae						
***Anemone* spp. (Anemone)**	**Anemone**	Ap	Aspirate by nose a juice mixture obtained pressing the following plants: anemone, red beet, cabbage, greater celandine, cyclamen, and onion	(Pignatari, 1894)	Pliny (*Naturalis Historia XXI, 94*). Galen (*De Materia Medica II, 207*).	(Plinio, 1985) (Kühn, 1829)
Delphinum staphysagria L. (Stavesacre)	Stafisagria	Ap	Chew stavesacre and pyrethrum	(Pignatari, 1894)	–	–
Rubiaceae						
***Coffea* spp. (Coffe)**	**Caffè**	Sd	Apply on forehead toasted and powdered coffee; Use suffumigations of coffee powder boiled in the water	(Pitrè, 1896; Bernoni, 1878)	–	–
Rhamnaceae						
Paliurus spina-christi Mill. (Christ's thorn)	Spina Christi	Lf	Put on the head pounded leaves of Christ's thorn	(Calvia, 1927)	–	–
Rutaceae						
***Citrus limon* (L.) Osbeck (Lemon)**	**Limone**	Ft	Apply on the forehead fresh or roasted sliced lemon	(Pitrè, 1896; Pignatari, 1894; De Nino, 1891; Bernoni, 1878)	–	–
***Ruta* spp. (Rue)**	**Ruta**	Ap	Bring on the head rue in a sack	(Adriano, 1932; Mancarella, 1930)	Pliny (*Naturalis Historia XX, 51*). Dioscorides (*De Materia Medica III, 45*). Galen (*Opera Omnia XII, 512, 514, 556, 558, 568, 569, 579, 581, 597; XIV, 500, 516, 543*).	(Plinio, 1985) (Kühn, 1829) (Kühn, 1826, 1827)
Santalaceae						
***Viscum album* L. (Mistletoe)**	**Vischio**	Ap	Drink decoction of mistletoe	(Zanetti, 1892)	Serenus Sammonicus (*Liber Medicinalis I, 17*)	(Pépin, 1950)
Solanaceae						
***Capsicum annum* L. (Pepper)**	**Pepe**	Ft	Apply on forehead powdered pepper mixed with an egg; Chew pepper with raisins	(Pitrè, 1896; Pignatari, 1894; Lombardi-Satriani, 1970)	–	–
***Hyoscyamus niger* L., *Hyoscyamus albus* L. (Henbane)**	**Giusquiamo**	Lf, Rt	Drink decoction of henbane root; Smear on the temples henbane leaves; put on the head fresh leaves of henbane	(Pedrotti and Bertoldi, 1930; Zanetti, 1892; Nardi, 1935)	–	–
Nicotiana tabacum L. (Tobacco)	Tabacco	Lf	Inhale snuff tobacco	(Pasquarelli, 1987; Ostermann, 1894)	–	–
***Solanum nigrum* L. (Black nightshade)**	**Solano**	Ap	Put on the head black nightshade	(Ferraro, 1885)	Hippocrates (*De Morbis III, 1*). Pliny (*Naturalis Historia XXVII, 44*). Galen (*Opera Omnia XII, 508, 509; XIV, 516*).	(Potter, 1988b) (Plinio, 1985) (Kühn, 1826, 1827)
***Solanum tuberosum* L. (Potato)**	**Patata**	Tb	Apply on forehead crude or roasted sliced potatoes	(Pitrè, 1896; Adriano, 1932; Lombardi-Satriani, 1970; Bertagnon, 1955)	–	–
Verbenaceae						
***Verbena officinalis* L. (Vervain)**	**Verbena**	Ap,Lf	Apply both on the temples and forehead leaves of vervain; Fasten forehead with vervain	(Coronedi-Berti, 1877; Finamore, 1894; Nardi, 1935)	Galen (*Opera Omnia XII, 575*).	(Kühn, 1826)
Vitaceae						

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Table 1 (*continued*)

Family/scientific/common name	Italian name	Plant parts	Route of administration	References	Historical sources	References
***Vitis vinifera* L. (Grapevine)**	**Vite**	Lf	Smear on the temples minced leaves of grapevine; Chew pepper with raisins	(Ostermann, 1894; Lombardi-Satriani, 1970; Pignatari, 1894)	Pliny (*Naturalis Historia XXIII, 3*). Dioscorides (*De Materia Medica V, 1*). Galen (*Opera Omnia XII, 508; XIV, 315*).	(Plinio, 1985) (Kühn, 1829) (Kühn, 1826, 1827)

Species names given in bold indicate those plants that nowadays show analgesic, anti-nociceptive, and anti-inflammatory properties.
Plant parts: Ap = Aerial parts; Fr = Flower; Ft = Fruit; Lf = Leaf; Rs = Resin; Rt = Root; Sd = Seed; Tb = Tuber.

botanic, zoological, anthropological and pharmacological points of view, could be the best way to try to identify natural remedies and diseases described in the ancient texts. Aliotta and colleagues (2003) stated that many scholars who have studied the Hippocratic texts generally agree on the identification of the plant-based prescriptions mentioned in the *Corpus Hippocraticum*. Such a result has been shown by Riddle (1987), who states that only 11 of 257 plants in the *Corpus Hippocraticum* cannot be identified with certainty. Moreover, projects such as GALEN, building semantic libraries for medical terminology, allow us to label medical terminology over the centuries (Buenz et al., 2004).

The data collected in this work show that the plant-based remedies utilized by Italian folk medicine for headache were prepared in several ways, usually depending on the plant used. Some of these methods included infusions, decoctions, fomentations, fumigations and macerations. Others included inhalation of powder or the juice of the plant. Treatments were administered by topical, oral and nasal routes. The most used route of administration was topical for which plants were mixed with vinegar, spirit, honey, olive oil, fat, butter, flour and albumen to increase penetration in the skin of the head. Sometimes, the remedies were given using, also, ritualistic objects or reciting prayers and formulas, while sometimes drawing symbols on the body (Romeo et al., 2015). This way represents a further link with the past. According to Karenberg and Leitz (2001), the ancient physicians did not distinguish between magic and medicine. The Egyptian medical papyri, for example, encompass not only what we define rational descriptions and prescriptions, but also magical and religious elements.

A large numbers of experimental studies have shown that plant compounds exerts anti-inflammatory effects through a variety of different mechanisms. Inflammation is the result of the interaction of a variety of inflammatory mediators, and cross mechanisms that exist between various mediators. Inflammatory cytokines and mediators are key components in the inflammation process; thus, inhibition of these targets is an efficient way to indirectly prevent the occurrence and development of inflammation and reduce the resulting damage (Wang et al., 2013).

From a pharmacological point of view, an overview of the recent literature reveals that a significant percentage (78.4%) of the plants, utilized by Italian folk healers in the late nineteenth and the early to mid-twentieth century to treat headache, contains components such as flavonoids, terpenoids and phenylpropanoids, which exhibit a large spectrum of anti-inflammatory, anti-nociceptive and analgesic activities. In fact, the results obtained by recent *in vivo* and *in vitro* studies have demonstrated that secondary metabolites show inhibitory activity against the NF-κB, NO, COX-2, TNF-α pathways which play an important role in triggering different types of headaches (Gorji, 2003; Capuano et al., 2009; Domingues et al., 2015; Reuter et al., 2002).

NF-κB is a transcription factor that can be induced by a wide variety of stimuli, including stress, bacteria, viruses, cytokines, and free radicals. It is a ubiquitous protein, composed mainly of two proteins, p50 and p65, that regulates the expression of genes encoding the pro-inflammatory cytokines, chemokines and inducible enzymes. (Baeuerle and Henkel, 1994). Among polyphenols extracted from *Vaccinium myrtillus* fruits, quercetin, epicatechin, and resveratrol were potent inhibitors of NF-κB activation in a human monocytic cell line (Karlsen et al., 2010). Crude extract of *Ruta graveolens* plant, the diethyl ether fraction and the isolated active compound, Rg 001 (3-(1′,1′-dimethylallyl) − 6-hydroxy-7-methoxy-chromen-2-one) repress activation of p65/NF-κB in LPS macrophage cells by inhibiting the activation of IkBα and effectively suppress nuclear translocation of NF-κB (Raghav et al., 2007). Finally, bioassay guided fractionation of the *Valeriana officinalis* extracts led to the isolation of acetylvalerenolic acid and valerenic acid, two sesquiterpenes active as inhibitors of NF-κB (Jacobo-Herrera et al., 2006).

NO is an important inflammatory mediator acting on vascular vasodilation and increasing permeability to facilitate the infiltration and

Table 2
Plants used by Italian folk medicine to treat headache, between the late nineteenth century and the early to mid-twentieth century, and their pharmacological properties at the present time.

Family/scientific/common name	Part of plant	Type of extract	Components	Experimental models	Animal or cell	Dose range	Minimal active concentration	Anti-inflammatory, analgesic pathways	Positive Controls	References
Adoxaceae										
Sambucus nigra L.	Fruit	Methanolic fraction	TP3	AA Enzyme-linked immunosorbent assay	-	10 μg/ml	-	COX-2	Indomethacin	Thole et al., 2006
(Elderberry)	Fruit	Acetone extract	TP4	AA Enzyme-linked immunosorbent assay	-	10 μg/ml	-	COX-2	Indomethacin	
Amarandaceae										
Beta vulgaris L. (Red beet)	Root	Ethanolic extract	-	Xylene-induced ear edema	Mice	200–400 mg/kg	400 mg/kg	-	-	Atta and Alkofahi, 1998
	Root	Ethanolic extract	-	Cotton pellet granuloma	Rats	200–400 mg/kg	400 mg/kg	-	-	
Amaryllidaceae										
Allium cepa L. (Onion)	Bulb	-	ALC-02	Carrageenan-induced paw edema	Rats	50–200 mg	200 mg	Anti-histaminic mediators	Ibuprofen	Kaiser et al., 2009
	Bulb	Fresh onion Juice	-	Carrageenan-induced paw edema	Rats	5–10 ml/kg	7.5 ml/kg	Cox	Diclofenac; morphine	Nasri et al., 2012
	Bulb	Fresh onion Juice	-	Hot Plate	Mice	5–10 ml/kg	7.5 ml/kg	-	Morphine	
	Bulb	Fresh onion Juice	-	Formalin test	Rats	-	7.5 ml/kg	Cox	Morphine	
Apiaceae										
Foeniculum vulgare Mill. (Fennel)	Fruit	Methanolic extract	-	Carrageenan-induced paw edema	Mice	-	200 mg/kg	COX; LOX	Indomethacin	Choi and Hwang, 2004
	Fruit	Methanolic extract	-	Arachidonic acid-induced ear edema	Mice	-	200 mg/kg	-	Indomethacin	
	Fruit	Methanolic extract	-	Formaldehyde-induced arthritis	Mice	-	200 mg/kg	-	Indomethacin	
	Fruit	Methanolic extract	-	Hot plate	Mice	-	200 mg/kg	-	-	
Pimpinella anisum L. (Anise)	Fruit	Ethanolic extract	-	LPS-stimolated	RAW 264.7 cells	50–250 μg/ml	72.7 μg/ml	NO	Indomethacin	Conforti et al., 2010
	Fruit	-	Trans-anethole	LPS-induced NO production	RAW 264.7 cells	50–250 μg/ml	102.7 μg/ml	NO	Indomethacin	
	Fruit	-	Limonene	LPS-induced NO production	RAW 264.7 cells	50–250 μg/ml	70.1 μg/ml	NO	Indomethacin	
Asteraceae										
Achillea millefolium L. (Yarrow)	Aerial parts Flower heads	-	Chamazulene carboxylic acid	Ear lobe edema	Mice	50 μM		COX-2	Nimesulide	Ramadan et al., 2006
	Aerial parts Flower heads	-	Chamazulene carboxylic acid	Carrageenan-induced paw edema	Rats	300 mg/kg		COX-2	Aspirin	
	Aerial parts Flower heads	-	Sesquiterpene Lactones	Respiratory burst assay	Human neutrophilis	-	500 μg/ml	-	Indomethacin	Choudhary et al., 2007
Arctium lappa L. (Burdock)	Seeds	Lignans	Lappaol F	LPS-induced NO production	RAW 264.7 cells	-	9.5 μM	NO	Aminoguanidine	Park et al., 2007
	Seeds	Lignans	Diarctigenin	LPS-induced NO production	RAW 264.7 cells		9.6 μM	NO	Aminoguanidine	
	Seeds	Lignans	Diarctigenin	LPS-induced NO production	RAW 264.7 cells	6–12 μM	8. μM	NO, PGE, IL, TNF-α	-	Kim et al., 2008
	Seeds	Lignans	Diarctigenin	Zimosan-induced NO production	RAW 264.7 cells	6–12 μM	9.6 μM	NO, PGE, IL, TNF-α	-	
Arnica montana L. (Arnica)	Flowers	Alcoholic extract	-	Carrageenan-induced paw edema	Rats	-	0.1 ml	-	-	Maĉedo et al., 2004
	Flowers	Alcoholic extract	-	Nystatin-induced paw edema	Rats	-	0.1 ml	-	-	

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Table 2 *(continued)*

Family/scientific/ common name	Part of plant	Type of extract	Components	Experimental models	Animal or cell	Dose range	Minimal active concentration	Anti-inflammatory, analgesic pathways	Positive Controls	References
	Flowers	Alcoholic extract	-	Histamina induced-vascular permeability	Rats	-	0.1 ml	-	-	
Artemisia absinthium L. (Wormwood)	Plant	-	Flavonoid p7F	LPS-stimulated	RAW 264.7	50–200 μg/ml	200 μg/ml	COX-2; PGE2;NO; NF-kB	Naringenin	Lee et al., 2004
Artemisia spp. (Artemisia)	Aereal pats	Essential oil	-	Formalin-induced hind-paw licking	Rats	10–300 mg/kg	100 mg/kg	-	Morphine	Maham et al., 2013
	Aereal pats	Essential oil	-	Hot plate test	Rats	10–300 mg/kg	100 mg/kg	-	Morphine	
	Aereal pats	Essential oil	-	Acetic acid- induced writhing test	Mice	10–300 mg/kg	10 mg/kg	PGE	Morphine; Naloxone	
	Aereal parts	Ethanolic extract	p-hydroxyacetophenone	Acetic acid- induced writhing test	Mice	20–500 mg/kg	100 mg/kg	TNF-α; IL-6; COX-2; NO	Indomethacin	Chou et al., 2012
	Aereal parts	Ethanolic extract	p-hydroxyacetophenone	Formalin-induced -paw licking	Mice	20–500 mg/kg	100 mg/kg	TNF-α; IL-6; COX-2; NO	Indomethacin	
	Aereal parts	Ethanolic extract	p-hydroxyacetophenone	Carrageenan-induced paw edema	Rats	20–500 mg/kg	100 mg/kg	TNF-α; IL-6; COX-2; NO	Indomethacin	
Glebonis coronaria (L.) Cass. ex Spach (Garland)	-	Lyophilized ethanolic extract	-	LPS-induced cells	P388D1 Murine monocyte	-	-	NO; TNF-α	-	Strzelecha et al., 2005
Helianthus annus L. (Sunflower)	Flower head	-	Diterpene acids	LPS-induced cells	RAW 264.7 Murine macrophages	1–20 μM	1 μM	COX-2; NOS-2		Diaz-Vicedo et al., 2008
	Flower head	-	Diterpene acids	TPA mouse-ear edema	Mice	0.25–1 mg/ear	0.25 mg/ear	-	Indomethacin	
Matricaria chamomilla L. (Chamomile)	Flower	Water extract	Apigenin	LPS-stimulated	THP1 macrophages	4–20 μM	4 μM	TNFα; IL	-	Drummond et al., 2012
Tanacetum balsamita L. (Costmary)	Aerial parts	Diethyl ether extract	-	Carrageenan-induced paw edema	Rats	25–100 mg/kg	25 mg/kg	-	Indomethacin	Karaca et al., 2009
Brassicaceae										
Brassica oleracea L. (Cabbage)	Aereal parts	Glucoside	Indol-3-carbinol	LPS-induced	RAW 264.7	12.5–100 μM	25 μM	NO; IL-6; IL-8	-	Jiang et al., 2013
Burseraceae										
Boswellia spp. (Incense)	Bark	Methanol extract		Hot plate test	Mice	200–400 mg/kg	400 mg/kg	-	Indomethacin	Mothana, 2011
	Bark	Methanol extract		Acetit acid-induced writhing test	Mice	200–400 mg/kg	400 mg/kg	-	Aspirin	
	Bark	Methanol extract		Cotton induced granuloma test	Rats	200–400 mg/kg	400 mg/kg	-	Indomethacin	
	Bark	Methanol extract		Carrageenan-induced paw edema	Rats	200–400 mg/kg	400 mg/kg	-	Indomethacin	
Cactaceae										
Opuntia ficus indica (L.) Mill. (Cactus pear)	Cladodes	Lyophilised extracts	-	IL-1β-induced	Human chondrocytes	200 μg/ml	-	NO; PGE-2	-	Panico et al., 2007
	Cladodes	Ethanol extract	B-Sitosterol	Adjuvant-induced pouch granuloma	Mice	14 mg/kg	-	-	Hydrocortisone	Park et al., 2001
Cannabaceae										
Humulus lupulus L. (Hop)	Hop pellet		Xanthohumol	LPS-induced	BV2 Mouse	0.5–5 μg/ml	2.5 μg/ml	NO; IL; TNF-α	-	Lee et al., 2011

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Table 2 *(continued)*

Family/scientific/common name	Part of plant	Type of extract	Components	Experimental models	Animal or cell	Dose range	Minimal active concentration	Anti-inflammatory, analgesic pathways	Positive Controls	References
					microglial cells					
Caprifoliaceae										
Valeriana officinalis L. (Valerian)	Root	Ethyl acetate extract	Valerenic acid	IL-6/Luc Assay	HeLa cells	-	100 μg/ml	NF-kB	-	Jacobo-Herrera et al., 2006
Crassulaceae										
Sempervivum tectorum L. (Common houseleek)	Leaves	Juice	Flavonolglycosides	Acetic Acid writhing test	Mice	720–2880 mg/kg	1440 mg/kg	-	-	Alberti et al., 2012
Cucurbitaceae										
Cucumis sativus L. (Cucumber)	Fresh fruit	Water extract	-	Tail immersion test	Mice	250–500 mg/kg	500 mg/kg	-	Diclofenac	Kumar et al., 2010
	Fresh fruit	Water extract	-	Acetic Acid writhing test	Mice	250–500 mg/kg	500 mg/kg	-	Diclofenac	
Ecballium elaterium (L.) A. Rich. (Squirting cucumber)	Fruit juice		Cucurbitacin B	Whittle method	Mice	50–400 mg/kg	200 mg/kg	-	Acetylsalicylic Acid	Yesilada et al., 1988
Cupressaceae										
Juniperus communis L. (Juniper)	Stem/fruits/leaves	Methanol/water extract	-	Carrageenan-induced paw edema	Mice	-	100 mg/kg	PGE-2	Indomethacin	Akkol et al., 2009
	Stem/fruits/leaves	Methanol/water extract	-	PGE2-induced hind paw edema	Mice	-	100 mg/kg	PGE-2	Indomethacin	
	Stem/fruits/leaves	Methanol/water extract	-	p-benzoquinone-induced writhing test	Mice	-	100 mg/kg	PGE-2	Acetylsalicylic acid	
	Stem/fruits/leaves	Methanol/water extract	-	Hot plate test	Mice	-	100 mg/kg	PGE-2	Morphin	
Ericaceae										
Vaccinium myrtillus L., *Vaccinium vitis idaea* L.	Fruit	Juice	-	Randomized controlled trial	Human volunteers	330 ml/day	-	IL-1 TNF-α	-	Karlsen et al., 2010
(Bilberry)	Fruit	-	Polyphenol	LPS-induced cells	U937 Human monocyte cell line	1-50μmol/l	25μmol/l	NF-kB	-	
Gentianaceae										
Gentiana lutea L. (Gentian)	Roots	Methanol extract	-	Swimming test	Mice	250–500 mg/kg	250 mg/kg	-	-	Öztürk et al., 2002
	Roots	Methanol extract	-	Tail-clip test	Mice	250–500 mg/kg	250 mg/kg	-	-	
	Roots	Methanol extract	-	Tail-immersion test	Mice	250–500 mg/kg	250 mg/kg	-	-	
Jungladaceae										
Juglans regia L. (Walnut)	Leaves	Ethanolic/acquaousextract	-	p-benzoquinone-induced writhing test	Mice	-	500 mg/ml		Acetylsalicylic acid	Erdemoglu et al., 2003
		Ethanolic extract	-	Carrageenan-induced paw edema	Mice	-	500 mg/kg		Indomethacin	
Hypericaceae										
Hypericum hircinum L. (Stinking tutsan)	Leaves	Methanolic extract	Quercetin	Forced swimming test	Mice	1–100 mg/kg	100 mg/kg	MAO	-	Chimenti et al., 2006
	Leaves	Methanolic extract	Quercetin	-	-	-	0.010 μM	MAO	Toloxatone	
Iridaceae										

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Table 2 *(continued)*

Family/scientific/common name	Part of plant	Type of extract	Components	Experimental models	Animal or cell	Dose range	Minimal active concentration	Anti-inflammatory, analgesic pathways	Positive Controls	References
Iris germanica L. (German iris)	Rhizomes	Methanolic extract		Formalin-induced paw edema	Rats	50–100 mg/kg	50 mg/kg		Dexamethasone	Ibrahim et al., 2012
	Rhizomes	Methanolic extract	Flavonoids	Formalin-induced paw edema	Rats	10 mg/kg	10 mg/kg		Dexamethasone	
Lamiaceae										
Lavandula angustifolia Mill., *Lavandula stoechas* L. (Lavender)	Leaves	Essential oil	-	Lavender essential oil inhalation	Human volunteers	15 min inhalation	-	-	-	Sasannejad et al., 2012
Marrubium vulgare L. (White horehound)	Aerial parts	-	Marrubiin	Microvascular leakage test	Mice	1–100 mg/kg	3 mg/kg	-	Diclofenac	Stulzer et al., 2006
Mentha pulegium L. (Pennyroyal)	Aerial parts	Hydro-ethanol extract	-	Carrageenan-induced ear edema	Mice	300 μl/cm^2	-	-	-	Moussaid et al., 2011
Origanum majorana L. (Marjoram)	Aerial part	Essential oil	Carvacrol	Carrageenan-induced mechanical hypernociception	Mice	25–100 mg/kg	50 mg/kg	TNF-α; NO;PGE2	Indomethacin	Guimaraes et al., 2012
	Aerial part	Essential oil	Carvacrol	Carrageenan-induced paw edema	Mice	25–100 mg/kg	25 mg/kg	TNF-α; NO;PGE2	Dexamethasone	
	Aerial part	Essential oil	Carvacrol	TNF-α-induced mechanical hypernociception	Mice	25–100 mg/kg	50 mg/kg	TNF-α; NO;PGE2	Indomethacin	
	Aerial part	Essential oil	Carvacrol	LPS-induced	Murine macrophages	1–100 μg/ml	1 μg/ml	TNF-α; NO;PGE2	-	
Rosmarinus officinalis L. (Rosemary)	Aerial parts	Hexane and ethyl acetate fractions	Carnosol/Betulinic acid	Carrageenan-induced murine pleurisy	Mice	-	2.5 mg/kg	NO; IL-1β; TNF-α	Dexamethasone Indomethacin	Benincá et al., 2011
	Aerial parts	Ethyl acetate fractions	Ursolic acid	Carrageenan-induced murine pleurisy	Mice	-	25 mg/kg	NO; IL-1β; TNF-α	Dexamethasone Indomethacin	
Salvia officinalis L. (Sage)	Leaves	Hydroalcoholic extract	-	Acetic acid writhing test	Mice	10–100 mg/kg	10 mg/kg	-	Ketoprofen	Rodrigues et al., 2012
	Leaves	Hydroalcoholic extract	-	Formalin test	Mice	3–100 mg/kg	3 mg/kg	-	Morphine Naxolone	
	Leaves	Hydroalcoholic extract	-	Glutamate-induced hind paw edema	Mice	3–100 mg/kg	3 mg/kg	-	-	
	Leaves	Hydroalcoholic extract	-	Capsaicin-induced paw edema	Mice	3–100 mg/kg	10 mg/kg	-	Ruthenium red	
	Leaves	Hydroalcoholic extract	-	Cinnamaldehyde-induced paw edema	Mice	3–100 mg/kg	10 mg/kg	-	Camphor	
Stachys officinalis (L.) Trevis. (Betony)	Aerial parts	Water extract	Iridoids	Carrageenan-induced paw edema	Rats	5 mg/kg	-	-	Diclofenac-Na	Háznagy-Radnai et al., 2012
Thymus serpyllum L. (Wild thyme)	-	-	Carvacrol	Carrageenan-induced paw mechanical hypernociception and edema	Mice	25–100 mg/kg	25 mg/kg	TNF-α NO	Dexamethazone	Guimarães et al., 2012
Thymus spp.	-	-	Carvacrol	TNF-α, dopamine, or PGE-2 induced mouse paw hypernociception	Mice	25–100 mg/kg	50 mg/kg	TNF-α NO	Indomethacin	
	-	-	Carvacrol	Carrageenan-induced	Mice	25–100 mg/kg	25 mg/kg	TNF-α NO	Indomethacin	

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Table 2 *(continued)*

Family/scientific/common name	Part of plant	Type of extract	Components	Experimental models	Animal or cell	Dose range	Minimal active concentration	Anti-inflammatory, analgesic pathways	Positive Controls	References
				pleurisy						
	-	-	Carvacrol	LPS-induced Nitrite production	Murine macrophages	1–100 μg/ml	1 μg/ml	TNF-α NO	-	
Lauraceae										
Laurus nobilis L. (Bay laurel)	Leaves	Essential oil	-	Tail-flick test	Mice	0.015–0.06 ml/kg	0.03 ml/kg	-	Morphine	Sayyah et al., 2003
	Leaves	Essential oil	-	Formalin-induced hind paw edema	Rats	0.125–0.25 ml/kg	0.25 ml/kg	-	Morphine	
	Leaves	Essential oil	-	Formaldehyde-induced hind paw edema	Rats	0.05–0.2 ml/kg	0.05 ml/kg	-	Piroxicam	
	Aerial parts	Water extract	-	LPS induced	BV2 murine macrophage cell line	0.02–0.6 μl/ml	0.02 μl/ml	COX-2; PGE2	Resveratrol	Orlando et al., 2010
Melanthiaceae										
Veratrum album L. (White hellebore)	-	-	Cis-resveratrol	LPS-induced cells	THP-1 macrophages	1–100 μM	1 μM	IL-1 COX-2	-	Huang et al., 2014
Oleaceae										
Olea europea L. (Olive)	Fruit	Olive Vegetation Water	-	LPS-treated	BALB7c Mice	5–125 mg/kg	35 mg/kg	TNF-α	-	Bitler et al., 2005
	Fruit	Olive Vegetation Water	-	LPS-induced	THP-1 monocytes	-	0.5 g/L	TNF-α	Dexamethasone	
Papaveraceae										
Chelidonium majus L. (Greater celandine)	Aereal parts	Methanol extract	-	Collagen-induced arthritis	Mice	40–400 mg/kg	400 mg/kg	TNF-α; IL-6	-	Lee et al., 2007
Fumaria officinalis L. (Fumitory)	Aerial Part	Ethanolic extract	-	Carrageenan-induced paw edema	Rats	100–400 mg/kg	100 mg/kg	-	Phenylbutazone	Rao et al., 2007
	Aerial Part	Ethanolic extract	-	Hystamin induced hind paw edema	Rats	100–400 mg/kg	100 mg/kg	-	Phenylbutazone	
	Aerial Part	Ethanolic extract	-	Cotton pellet induced granuloma	Rats	100–400 mg/kg	100 mg/kg	-	Phenylbutazone	
	Aerial Part	Ethanolic extract	-	Hot plate	Mice	100–400 mg/kg	200 mg/kg	-	Phenylbutazone	
	Aerial Part	Ethanolic extract	-	Acetic acid writhing test	Mice	100–400 mg/kg	100 mg/kg	-	Acetylsalicylic acid	
Plantaginaceae										
Plantago spp. (Plantain)	Leaves/seeds	Methanolic extract	-	Acetic acid writhing test	Mice	200–400 mg/kg	400 mg/kg	-	Dipyrone	Atta and Abo El-Sooud, 2004
	Leaves	Methanolic extract	-	Tail-flick test	Mice	200–400 mg/kg	400 mg/kg	-	Dipyrone	
	Aerial parts	Hydromethanolic extract	-	LC-MS/MS	Human platelets	1–9 mg/ml	0.65 mg/ml	COX-1 12-LOX	Acetylsalicylic acid; Quercetin	Beara et al., 2010
Poaceae										
Avena sativa L. (Oat)	Whole grain	-	-	NF-kB inhibitory assay	Human 293 T cells	-	2 mg/ml	NF-kB	-	Chu et al., 2013
Triticum spp. (Wheat)	Whole meal flour	Hydrophilic extract	Phenolic acid	LPS-stimulated cells	HT-29 Human intestinal cells	8.2–66 μg/ml	66 μg/ml	IL-8	-	Laddomada et al., 2015
	Whole meal flour	Lipophilic extract	Isoprenoids	LPS-stimulated cells	HT-29 Human intestinal cells	0.01–0.2 μg/ml	0.2 μg/ml	IL-8	-	
Portulacaceae										
Portulaca oleracea L. (Verdolaga)	Aerial parts	Ethanolic extract	-	Hot-plate test	Mice	200–400 mg/kg	400 mg/kg	-	Diclofenac	Chan et al., 2000

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Table 2 *(continued)*

Family/scientific/common name	Part of plant	Type of extract	Components	Experimental models	Animal or cell	Dose range	Minimal active concentration	Anti-inflammatory, analgesic pathways	Positive Controls	References
	Aerial parts	Ethanolic extract	-	Tail-flick test	Rats	200–400 mg/kg	400 mg/kg	-	Diclofenac	
	Aerial parts	Ethanolic extract	-	Carrageenan-induced paw edema	Rats	200–400 mg/kg	200 mg/kg	-	Diclofenac	
	Aerial parts	Ethanolic extract	-	Cotton pellet induced granuloma	Rats	200–400 mg/kg	400 mg/kg	-	Diclofenac	
Primulaceae										
Cyclamen spp. (Cyclamen)	Dried Tubers	Petroleum ether/methanol/chloroform extracts	-	Carrageenan-induced paw edema	Rats	75–150 mg/kg	75 mg/kg	-	Indomethacin	Speroni et al., 2007
	Dried Tubers	Petroleum ether/methanol/chloroform extracts	-	Acetic acid writhing test	Mice	50–100 mg/kg	150 mg/kg	-	Morphin	
Ranunculaceae										
Anemone spp. (Anemone)	Rhizome	Saponins	Raddeanoside R1, Raddeanoside F, Raddeanoside H	Acid acetic-induced pain reaction	Mice	-	125 mg/kg	-	-	Sun et al., 2011
Rubiaceae										
Coffea spp. (Coffe)	Unroasted beans	Diterpenes	Cafestol; Kahweol	Cell based assay for inhibition of COX-2 activity	RAW 264.7	0.25–5.0 μg/ml	-	COX-2	-	Muhammad et al., 2008
Rutaceae										
Citrus limon (L.) Osbeck	Leaves	Essential oil	Mono terpenes	Acetic acid-induced writhing	Mice	50–150 mg/kg	50 mg/kg		Morphine	Campelo et al., 2011
(Lemon)	Leaves	Essential oil	Mono terpenes	Formalin test	Mice	50–150 mg/kg	100 mg/kg		Morphine; Aspirin	
	Leaves	Essential oil	Mono terpenes	Hot plate test	Mice	50–150 mg/kg	-		Morphine	
Ruta spp. (Rue)	Aerial parts	Polyphenolic/Alkaloid fraction	-	Carrageenan-induced paw edema	Rats	5–15 mg/kg	5 mg/kg	COX-2; 5-LOX	Diclofenac	Ratheesh et al., 2010
	Aerial parts	PhenolicAlkaloid fraction	-	Adjuvant-induced hind paw arthritis	Rats	10 mg/kg	-	COX-2; 5-LOX	Indomethacin	
	Whole plant	Methanolic extract	-	LPS-stimulated	J774A.1 murine macrophage cells	300–500 μg/ml	300 μg/ml	TNF-α; IL; NF-kB	L-NAME	Raghav et al., 2007
	Whole plant	Methanolic extract	3-(1'−1'-dimethyl-allyl)−6-hydroxy-7-methoxy-coumarin	LPS-induced	BALB/c mice	1 mg/25 g	-	NO; IL	-	
Santalaceae										
Viscum album L. (Mistletoe)	Leaves and stems	Ethyl acetate fraction	Isoflavonoids	P-bencoquinone-induced writhing test	Mice	125–250 mg/kg	125 mg/kg	-	Acetylsalycilic acid	Orhan et al., 2006
	Leaves and stems	Ethyl acetate fraction	Isoflavonoids	Carrageenan-induced hind paw edema	Mice	125–250 mg/kg	125 mg/kg	-	Indomethacin	
Solanaceae										
Capsicum annum L. (Pepper)	Fruit	Petroleum ether extract	Carotenoids	Acetic acid-induced writhing	Mice	5–80 mg/kg	5 mg/kg	-	Ibuprofen	Hernandez-Ortega et al., 2012
	Fruit	Petroleum ether extract	Carotenoids	Hot plate test	Mice	5–80 mg/kg	80 mg/kg	-	Indomethacin	
	Fruit	Petroleum ether extract	Carotenoids	Carrageenan-induced paw edema	Mice	5–80 mg/kg	5 mg/kg	-	Indomethacin	
Hyoscyamus niger L., *Hyoscyamus albus* L. (Henbane)	Seeds	Methanolic extract	-	Hot plate test	Mice	100–400 mg/kg	100 mg/kg	-	Pentazocine	Begum et al., 2010
	Seeds	Methanolic extract	-	Acetic Acid writhing	Mice	100–400 mg/kg	200 mg/kg	-	Acetylsalicylic acid	

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Table 2 *(continued)*

Family/scientific/ common name	Part of plant	Type of extract	Components	Experimental models	Animal or cell	Dose range	Minimal active concentration	Anti-inflammatory, analgesic pathways	Positive Controls	References
				test						
	Seeds	Methanolic extract	-	Carrageenan-induced paw edema	Rats	50–200 mg/kg	50 mg/kg	-	Phenilbutazone	
	Seeds	Methanolic extract	-	Cotton pellet induced granuloma	Rats	100–400 mg/kg	100 mg/kg	-	Indomethacin	
Solanum nigrum L. (Black nightshade)	Leaves	Chloroform extract	-	Acetic Acid writhing test	Mice	20–200 mg/kg	20 mg/kg	-	Acetylsalycilic acid	Zakaria et al., 2006
	Leaves	Chloroform extract	-	Hot plate-test	Mice	20–200 mg/kg	20 mg/kg	-	Morphine	
	Leaves	Chloroform extract	-	Fomalin-test	Rats	20–200 mg/kg	20 mg/kg	-	Acetylsalycilic acid	
	Leaves	Chloroform extract	-	Carrageenan-induced paw edema	Rats	100–200 mg/kg	100 mg/kg	-	Acetylsalycilic acid	
Solanum tuberosum L. (Potato)	Tuber	Ethanolic extract	-	Formali-induced paw licking test	Mice	100–200 mg/kg	100 mg/kg	-	Aminopyrine	Choi and Koo, 2005
	Tuber	Ethanolic extract	-	Acetic Acid writhing test	Mice	100–200 mg/kg	100 mg/kg	-	Aminopyrine	
	Tuber	Ethanolic extract	-	Hot plate-test	Mice	100–200 mg/kg	100 mg/kg	-	Aminopyrine	
	Tuber	Ethanolic extract	-	Carrageenan-induced paw edema	Mice	100–200 mg/kg	100 mg/kg	-	Indomethacin	
	Tuber	Ethanolic extract	-	Arachidonic acid-induced ear edema	Mice	100–200 mg/kg	100 mg/kg	-	Indomethacin	
Verbenaceae										
Verbena officinalis L. (Vervain)	Leaves	Methanolic extract	-	Carrageenan-induced paw edema	Rats	1–3% (50% Methanolic extract)	1%	-	Piroxicam	Calvo, 2006
	Leaves	Methanolic extract	-	Formalin test	Rats	1–3% (50% Methanolic extract)	2.5%	-	Methyl salycilate	
Vitaceae										
Vitis vinifera L. (Grapevine)	Leaves	Water extract	-	Carrageenan-induced hind paw edema	Mice	100–400 mg/kg	100 mg/kg	-	Indomethacin	Kosar et al., 2007
	Leaves	Water extract	-	P-benzoquinone-induced writhing test	Mice	100/400 mg/kg	100 mg/kg	-	Acetylsalycil acid	

penetration of inflammatory mediators, pain substances into the inflammatory site (Wang et al., 2013). Two known lignans, lappaol F, and diarctigenin, isolated from *Arctium lappa* seeds, strongly inhibited NO production in the LPS-stimulated RAW264.7 cells (Park et al., 2007).

TNF-α is one of the major pro-inflammatory cytokines that activates monocyte–macrophage cells to release large amounts of IL-1, IL-6, IL-8, PGE_2 and other inflammatory mediators and stimulate a chain reaction of inflammation (Wittmann et al., 1996).

Indol-3-carbinol (I3C) is an autolysis product of glucosinolate present in Brassica plants. I3C reduced the amounts of IL-6 and TNF-α in broncho-alveolar lavage fluid and in the acute lung injury in the LPS-induced mouse model (Jiang et al., 2013). Carnosol, betulinic acid and ursolic acid, isolated from crude extract of *Rosmarinus officinalis* aerial parts have been showed an important anti-inflammatory activity by inhibition not only of leukocytes and exudation, but also of a pro-inflammatory enzyme and mediators (NOx, IL-1b, and TNF-α) in carrageenan-induced murine pleurisy (Benincá et al., 2011). p7F (5,6,3',5'-tetramethoxy 7,4'-hydroxyflavone), a flavonoid extracted from the aerial parts of *Artemisia absinthium*, markedly inhibited PGE_2 activity in LPS-induced macrophages, as shown by Lee and colleagues (2004).

COX-2 belongs to the cyclooxygenase family which are key enzymes of the arachidonic acid cascade (Ramadan et al., 2006). In resting cells, it is not expressed; however, after stimulation by an inflammatory response, COX-2 can be synthesized quickly and is involved in inflammatory processes (Wang et al., 2013).

Three diterpene acids: grandiflorolic, kaurenoic and trachylobanoic acids extracted from *Helianthus annuus* flower head showed inhibition of the expression of COX-2 and the release of inflammatory cytokines in LPS-activated RAW 264.7 macrophages (Díaz-Viciedo et al., 2008).

In addition, MAO inhibitors, usually, are used in the cure of depression and other psychological disorders. They increase the concentration of neuroamines, especially 5-HT and NE. Vasodilatation, which is a source of pain in headache (Shevel, 2011), is inhibited by the depletion of the aforesaid neuroamines. For these reasons, the use of MAO inhibitors is reserved for chronic daily headache patients whose symptoms have not been relieved by conventional prophylactic treatment (Redillas and Solomon, 2000). Extracts from leaves of *Hypricum hircinum* showed MAO-A inhibitory activities. Quercetin showed a selective MAO-A inhibitory activity in the forced swimming test (Chimenti et al., 2006)

Moreover, essential oil from lavender has been studied in a placebo-controlled clinical trial. In this study, the percentage of responders was significantly higher in the lavender cohort than in the placebo cohort, so the inhalation of lavender essential oil may be an efficacious and innocuous route of administration in acute management of migraine headache and his associated symptoms such as photophobia, phonophobia, nausea and vomiting (Sasannejad et al., 2012).

Finally, metabolites isolated from anemone, arnica, red beet, incense, pepper, lemon, cucumber, cyclamen, squirting cucumber, fumitory, gentian, henbane, German iris, walnut, marjoram, pennyroyal, verdolaga, sage, common houseleek, black nightshade, potato, betony, costmary, vervain, mistletoe and grapevine have showed a more generic central and/or peripheral depressant action whose mechanisms are not readily apparent.

Although most, if not all of the plant-based compounds are still in the pre-clinical phase, we speculate that Italian folk medicine exerting anti-headache effect may mainly act through the regulation of Nitric Oxide, Histamine, Serotonin and Arachidonic Acid pathways. Besides, as a holistic medicine, bioactive compounds, isolated from the plants utilized by Italian healers between the late nineteenth century and the early to mid-twentieth century, could be helpful not only to cure headache, but also for the treatment of some other diseases which exhibit an inflammatory component such as cancer, rheumatoid arthritis, sepsis, atherosclerosis and Alzheimer's disease (Calixto et al., 2003, 2004).

5. Conclusions

Folk medicine, based on centuries of experience, is like an uncontrolled laboratory which, if examined carefully and critically, would help us to gain valuable information to be exploited in modern medicine.

Besides historical prospective, this study unearths interesting remedies that can provide a comprehensive basis to perform further investigations for the development of effective drugs against headache.

Even if traditional knowledge about natural remedies to treat several diseases was handed down almost entirely orally, it has been the subject of historical documents, too. These valuable sources, nowadays, should be explored systematically.

The award of the 2015 Nobel Prize for Physiology or Medicine to Prof. Youyou Tu for her discovery and development of artemisinin that is the most effective drug against malaria, gives us a lesson: sometimes it is needed to look back, to look forward.

Competing interests

The authors declare that they have no competing interests.

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