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Review

Medicinal herbs for the treatment of rheumatic disorders—A survey of European herbals from the 16th and 17th century

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ABSTRACT

Ethnopharmacological relevance: From the 16th up into the 18th century botanical and medicinal knowledge in Europe was documented and spread in magnificently illustrated herbals. For the most part modern science has neglected this source of knowledge and old remedies have not been systematically evaluated pharmacologically.
Aim of the study: Rheumatic disorders and chronic inflammatory and degenerative diseases of the musculoskeletal system were chosen in an attempt to discuss remedies described in the old herbals in the viewpoint of modern science.
Materials and methods: Five of the most important European herbals of the 16th and 17th century were searched for terms related to rheumatic diseases, and plants and recipes described for their treatment. An extensive search of the scientific data banks Medline and SciFinder scholar was done to find recent results concerning the phytochemistry and possible antiphlogistic activities of the plants.
Results: Sixty-three plants were identified in the herbals for this indication. More than half of them have shown *in vitro* or *in vivo* antiphlogistic activities.
Conclusions: European herbals may be a valuable source of information for the selection of plants for focussed screening programmes. Information contained in these herbals should be explored in a systematic manner.

Contents

Abbreviations: ASS, acetylsalicylic acid; COX, cyclooxygenase; LOX, lipoxygenase; LTB_4, leukotriene B_4; nF-κB, nuclear factor κB; NSAR, non-steroidal anti rheumatics; IL, interleukins; PGE_2, prostaglandin E_2; PLA_2, phospholipase A_2; TNF, tumour necrosis factor; OA, osteoarthritis; RA, rheumatoid arthritis; TCM, traditional Chinese medicine.

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1. Introduction

The 15th century was a time of great social and technological change. Long voyages were waged and unknown continents discovered, technological innovation, a marked increase of writings outside protective monastic walls and first flourishing of humanistic ideas and religious reforms. It was in this time and age that Johannes Gensfleisch zur Laden zum Gutenberg introduced the printing press with movable metal types. Henceforth knowledge and ideas were no longer confined to ones immediate surroundings, but could be documented and circulated hundred and thousand fold. Medical practises and the knowledge of medicinal herbs were compiled in a number of herbals which soon became some of the best selling books of their time. With their scientific descriptions and their medicinal information they became the predecessors of pharmacopoeias and science books.

Despite the once wide use of these old herbals produced in many editions for centuries, modern science has barely started to scientifically explore this florilegium. When "European herbal medicine" is entered in the database of SciFinder a mere 2 citations are found. "Traditional European medicine" gives 7 hits. On the other hand, a search for the corresponding Asian terms "TCM" (traditional Chinese medicine) and Ayurveda in the database of SciFinder gave 4264 and 550 references, respectively, with a strong increase in recent years (data accessed on June 5, 2008). The only mention of the authors of the 16th century herbals are when the plant genera which were named in their honour are mentioned: Lonicera: Caprifoliacae; Tabernaemontana: Apocynaceae; Matthiola: Brassicaceae; Fuchsia: Onagraceae; Tragia: Eurphorbiaceae (Bock was also called Tragus). When one looks for such terms in everyday internet search engines like www.google.com the differences are just as striking.

One of the reasons for neglecting these works is certainly their poor accessibility nowadays. Original herbals usually cannot be easily accessed, or if so, cannot be removed from their safe libraries. Some committed historians have taken the effort of photographically documenting entire herbals and making them accessible on the internet, so their can now be studied online (for example: http://imgbase-scd-ulp.u-strasbg.fr./displayimage.php?album=24&pos=0&visiblePos=1). However marvellously illustrated these beautiful works may be, they are difficult to read, lack proper pagination and are nearly impossible to understand for those not familiar with the illustrious historic phrasing, fonts, grammar and spelling. In certain cases parts of herbals have been digitalised and put online (for example: http://www.kraeuter.ch/). Some contemporary researchers have provided detailed cultural-historical assays on the use and understanding of individual plants (see for example: Mayer and Czygan, 1999, 2000a,b; Fiore et al., 2005).

Studying these books may be highly rewarding indeed. One just has to look at the amount of scientific and popular attention traditional Chinese medicine (TCM) has been attracting lately. Using traditional medicinal knowledge in drug discovery seems so promising that recently even large Pharmaceutical Companies have begun to show interest. Novartis, a Swiss drug giant, for example, has invested 100 million US dollars in a new research and development centre in Shanghai that will bring together modern biomedical research and millennia old medicinal concepts (Stone and Xin, 2006). It is also Novartis – in collabortaion with the world health organisation (WHO) – that produces and distributes Coartem® (Riamet®) a front line antimalarial drug. Coartem is derived from quinghausu (artemisinin) a sesquiterpene peroxide first isolated from the TCM herb *Artemisia annua* L. by Chinese scientists in 1971 (see White, 2008). In 2006, more than 62 million Coartem treatment courses delivered to more than 30 countries,

saving an estimated 200 000 lives (Novartis, 2008). So we see clearly that scientific examination of historic works can be the base for the "rediscovery" of long forgotten remedies and a source of information for a more focussed screening for new leads.

This survey is a starting point in our study of European herbals from the 16th and 17th century. We focussed on remedies used for rheumatic disorders for a number of reasons: rheumatic disorders and chronic inflammatory and degenerative diseases of the musculoskeletal system were widespread in the 16th and 17th centuries just as they are today so the indication is clear and recognisable in the books. Molecular targets are known and a number of *in vivo* and *in vitro* test systems have been established making a meaningful pharmacological study of the remedies possible. Also, quite a number of purified natural products have been tested in such assays allowing for phytochemical discussion (Adams and Bauer, 2008).

2. Methodology

We had access to four original herbals: Bock, 1577, Matthiolus, 1590, Lonicerus, 1770, Tabernaemontanus, 1687 and one facsimile: Fuchs, 1543, which are kept at the Swiss Pharmaceutical museum in Basel. These books were amongst the most important European herbals of the 16th and 17th century. The 18th century herbal by Lonicerus (1770) is a supplemented and illustrated version of the original 16th century edition. The herbals were searched for terms related to rheumatic diseases, and plants and recipes described for treatment. The term "rheumatism" is frequently used in colloquial speech and historical contexts, but no longer in medical literature as it does not describe one specific recognised disorder, but rather a multitude of diseases. In the herbals of the 16th and 17th century the word "rheumatism" is not either used, so the indices of the five herbals were systematically searched for the old German terms: "Gicht" "Gegicht", (gout) "Glied(er)weh" (pains of the joints), "Gliedsucht" (ailments of the limbs), "Gesüchte" or "Gesichte" (grievances and ailments), "Gleichenweh" (gout in the joints), "Zipperlein" (twitching), "Podagra" (gout of the feet) and "Hüfftweh" (pains in the hips). We would like to stress the point that it is not enough just to merely run a search for these terms. It is necessary to read the texts carefully and understand them, because certain terms may be used in different contexts at different occasions. Plants that were recommended for these ailments were recorded. Obviously the books discussed here were written long before Carl von Linné (Linnaeus) published his Systema Naturae (1st edition in 1735) and established our binominal taxonomic system, so any claim to taxonomic impeccability on our side is out of place, but commonly old plant names in the herbals resemble the German or Latin names used in various previous times up until today or those used in distinct geographic regions. Comprehensive listings of such names can be found in the "Wörterbuch der Deutschen Pflanzennamen" by Marzell (2000). The detailed coloured illustrations of the individual plants in the herbals also gave strong evidence of the identity of the plants at a species level. We have included photographs of the plant illustrations, their historic names and common German names in the supporting information. Generally they resemble the illustrations in modern plant guides quite well (see for example: Jäger and Werner, 2005; Lauber and Wagner, 2007; Spohn et al., 2008) and can be recognised by a trained botanist.

Unfortunately clinical data is very scarce for herbal medicines. Available good scientific data is mostly *in vitro* and *in vivo* data from a number of antiphlogistic assays. Amongst the anti inflammatory *in vitro* assays the ones examining the effects of an extract or compound on arachidonic acid metabolising enzymes are the most commonly used. Arachidonic acid forms the substrate of different oxygenases such as cyclooxygenases (LOX), monooxygenases and lipoxygenases (LOX), leading to the so-called eicosanoids. The release of AA from cell membrane phospholipids is the result of activation of phospolipase A_2 or C by cell stimulation.

Leukotrienes (LTs) are eicosanoids synthesised in the first metabolic step by 5-lipoxygenase (5-LOX) from 20 carbon fatty acids—predominantly arachidonic acid. They are potent mediators of inflammation. They include the cysteinyl leukotrienes LTC_4, LTD_4, LTE_4, which cause bronchoconstriction, chemotaxis and enhanced blood vessel-permeability, and therefore play a major role in asthma, and the dihydroxyeicosatetraenoate LTB_4, an important mediator for acute and chronic inflammatory ailments. Cyclooxygenases (COX) are enzymes which catalyse cyclic peroxidation of arachidonic acid which is then further processed to the prostaglandins (PGs), prostacyclines and thromboxan. There are two different forms of cyclooxigenases: COX1 is the constitutive physiological form and COX2 is induced in inflammation and other tissue damage. Most commonly the effects of a test substance or extract are studied in assay systems which contain these targets either as pure enzymes or in expressing cell systems such as macrophages, leucocytes and T-cells. Other test systems cover nuclear factor κB (NF-κB), tumour necrosis factor (TNF_α) and interleukins (IL), which are less inflammation specific targets and also act as mediators of various other diseases (Pairet and Van Ryn, 1998; Miyazaki et al., 2007; Adams and Bauer, 2008).

A number of anitinflammatory *in vivo* test systems in mice and rats have been developed. Hereby proinflammatory substances like carrageenan, arachidonic acid or xylen are injected into paws or applied to ears to induce inflammatory reactions and swelling. An antiinflammatory substance should reduce the swelling of the affected organ compared to control. This is measured with a plethysmograph, a micrometer device of by weighing punched out bits of ears. Variation of the oedema inducing agents helps model different types of chronic and acute inflammation (Cooper, 2007; Pretorius, 2008). For practical and methodological reasons these assays mostly apply acute inflammatory models like carrageenan, arachidonic acid induced oedema, rather than chronic ones like adjuvans induced rat paw oedema.

An extensive search of the scientific data banks Medline and SciFinder scholar was done to find recent results concerning the phytochemistry and possible antiphlogistic activities of the plants, by running searches with the plant names and terms like rheumatism, inflammation, COX, LOX, NF-κB, interleukins and TNF_α (Adams and Bauer, 2008).

2.1. General information on herbals and their authors

The actual titles of the herbals – which are expansive and verbally challenging to say the least – are given in the supporting information. The title of Lonicerus, for example, expands over 200 words and 1351 letters! To make things easier the herbals used for this study will be abbreviated in the following manner:

Bo.	Bock (1577)
Fu.	Fuchs (1543)
Matt.	Matthiolus (1590)
Lon.	Lonicerus (1770)
Tab.	Tabernaemontanus (1687)

Here is brief overview of the lives and their accomplishments of the herbals authors:

Hieronymus Bock (*1498–†21 February 1554 in Hornbach, Germany). As the personal physician to Duke Ludwig II in Zweibrücken and parish priest in Hornbach he was a renowned man of his time. His botanic, medical and pharmacological studies lead to the esteemed "*Kreütter Buch*" in 1539 which was quite revolutionary

due to the precise descriptions of plants. Up into the 17th century Bock's herbal was a valued reference for many generations of scholars and reappeared in numerous editions. Due to his studies and his "*Kreütter Buch*" Hieronymus Bock can be seen as one of the fathers of botany.

Leonhart Fuchs (*17 January 1501 in Wemdingen–†1566 in Tübingen, Germany). During his years as a medical attendant to the Earl of Anbach Mark Graf Georg "des Frommen" (George the pious), Fuchs studied the ancient writings of Hippocrates, Dioscurides and Galen. Later on as a professor of medicine at Tübingen University he dramatically reformed the entire curriculum, using only original antique medicinal writings, organising botanical excursions for prospective physicians to study living objects on site. He founded one of the first botanical gardens. Fuchs's first writing "*De Historia Stirpium commentarii insignes*" which he published in Latin 1542, as well as the German Version "*New Kreüterbuch*" which appeared in 1543 were revolutionary for their time with methodical descriptions of the plants, with detailed descriptions of habitats, flowering times and medicinal uses. Alongside Hieronymus Bock Leonhart Fuchs must also be regarded as one of the fathers of Botany.

Pietro Andrea Mattioli, lat. *Matthiolus* (*23 March 1501 in Siena–†1577 in Trient, Italy). During his time helping the terminally ill in Rom Matthiolus also performed numerous botanical studies, and during his time as a physician in Triente he got familiar with the flora of the southern Alps. As of 1554 he was the personal physician of first archduke Ferdinand II, and later emperor Maximillian II in Prague. His herbal – opulently illustrated with detailed woodcuts – was first released in 1554 in Latin. The herbal gained great popularity and appeared in over 60 editions in German, French and Czech. It described many Mediterranean plants, which were hardly known to the German speaking world back then.

Adam Lonitzer, lat. *Lonicerus* (*10 October 1528 in Marburg–†29 Mai 1586 in Frankfurt am Main, Germany). Lonicerus was a professor of mathematics and a town physician. Starting in 1550 be busied himself with herbals gathering information from authors of his time (Bock, Fuchs, Matthiolus etc.) and from ancient scholars like Dioscurides and Galen. This resulted in a rather heterogeneous writing that first appeared 1557. It describes endemic and exotic plants alongside real and fantastic creatures, metals, minerals, horticulture and the craft of distilling.

Jacob Theodor (*1522 in Bergzabern–†August 1590 in Heidelberg, Germany) became known as *Tabernaemontanus*, which indicates his home town of Bergzabern, Germany. Tabernaemontanus can be considered one of the greatest botanists of the 16th century. He was in contact with the most important natural historians of his time like Hieronymus Bock, Leonhard Fuchs, Otto Brunfels, Adam Lonitzer and others. These encounters and earlier sources of knowledge like Dioscurides, Galen etc. influenced his work. In 1588 he first published his main writing, the "*New Kreuterbuch*".

3. Results

3.1. Organisation of the data

Plants are listed alphabetically by plant families and within these by genera (Table 1). We have given a very brief description of how the plant was used. Because our literature sources are not available to most readers we have listed all the recipes referred to here as supporting information unaltered in the original wording. More recent scientific results relevant to the use described in the herbals are then discussed. Fourteen of the preparations described here were a kind of schnaps, a strong distilled alcoholic beverage. We shall use the term schnaps throughout this survey because we think the technical terms distillate and the derogatory term booze do not adequately describe the complex preparations.

3.2. Anacardiaceae

Matt. cites Tab. in recommending the sap of *Pistacia terebinthus* L. (Terebinth) made into pills for the treatment of hip pains, gout of the feet and of the hands.

Pistacia terebinthus is a shrub or small tree from the Mediterranean countries. The two drugs traditionally obtained from it are turpentine and its galls. Turpentine is a sappy balm from the trees bark which contains 10–14% essential oils. The galls contain tannins, gallic acids, sap and essential oils (Font Quer, 1993).

Oleanolic- and oleanonic acid, two triterpenes from *Pistacia terebinthus* galls were tested in a number of *in vivo* inflammation models (Giner-Larza et al., 2001). In ethylphenylpropiolate- and TPA-induced mice ear oedema oleanolic acid showed no significant antiphlogistic activity, but in the DPP-induced mouse ear oedema inhibition by oleanonic acid was comparable to carbamazepine. In a chronic inflammation (model-mouse ear oedema induced by multiple application of TPA-oleanonic) acid was active whilst oleanolic acid was inactive. Oleanonic acid inhibited LTB_4-production in a dose dependant manner (IC_{50} = 17 μM), whereas oleanolic acid weakly inhibits 5-LOX (30% inhibition at 100 μM). This might explain the activity of oleanonic acid in the *in vivo* model, where oleanolic acid was inactive. In PLA_2-induced paw oedema both oleanolic and oleanonic acid were active. Oleanonic acid reduced bradykinin-induced paw oedema significantly and had a similar activity as isoprenalin (Giner-Larza et al., 2002).

The galls of *Pistacia terebinthus* also contain tetracyclic antiphlogistic triterpenes called lanostanes (Jain et al., 1995; Ansari and Ali, 1996; Cuéllar et al., 1996). A methanolic extract of *Pistacia terebinthus* and the three triterpenes masticadienolic, masticadienonic and morolic acid were tested *in vivo*. The methanolic extract inhibited multiple TPA induced mouse ear oedema significantly, but did not show significant activity in an acute TPA-model. All three triterpenes also reduced the swelling in the chronic model significantly. The extract inhibited *Naja naja*-PLA_2-induced paw oedema significantly after 30 and 60 min by 67 and 61%, respectively, however lost their activity after 90 min. The extract also inhibited *Naja mossambica* PLA_2 induced paw oedema, as did the three triterpenoids (Giner-Larza et al., 2000).

Possibly the mechanism of action for *Pistacia terebinthus* triterpenes could be direct inhibition of 5-LOX, as has been shown by the somewhat similar boswellic acid from *Boswellia* species (Ammon, 2006).

3.3. Apiaceae

Tab. praised the common European plant *Aegopodium podagraria* L. (Ground elder) in his eyes a "despised and unlovely weed" for its remarkable medicinal value for gout and joint pains. Tab. recommends cooking *Aegopodium podagraria* in wine, which is to be drunk twice a day in both morning and evening. This should heal gout of the feet and as hip pains. Ground elder has been traditionally used in Europe in folk and monastic medicine for gout and similar ailments known as podagra. This led to it being named *Aegopodium podagraria* (Duke et al., 2002). *Aegopodium podagraria* contains the polyacetylene falcarindiol, which in an *in vitro* study by Prior et al. (2007) inhibited COX-1 with an IC_{50} of 0.3 μM (IC_{50} indomethacin = 9 μM). Falcarindiol is active against 12-LOX and 15-LOX. The plant contains some essential oil (Paramonov et al., 2000) and lectins (Peumans et al., 1985) but other than this little is known about the phytochemistry of this common Apiaceae.

According to Bo., Matt. and Tab. *Foeniculum vulgare* Mil. (Fennel) should be eaten to expel tough slime, which was viewed to be the source of rheumatism according to the theory of humoral pathology.

Table 1
Plant species found in the five 15th and 16th century herbals for rheumatic disorders, listed by alphabetically by family.

Plant species	Plant family	Mentioned by[a]	Historic citations[b]	Use[c]	Citations[d]	*In vitro* data[e]	*In vivo* data[f]
Pistacia terebinthus	Anacardiacaeae	Matt., Tab.	2	I	12	+	+
Aegopodium podagraria	Apiaceae	Tab.	1	I+E	5	+	–
Foeniculum vulgare	Apiaceae	Bo., Matt., Tab.	3	I	6	+	+
Peucedanum ostruthium	Apiaceae	Bo., Fu., Matt., Tab.	4	I+E	1	–	+
Pimpinella saxifraga	Apiaceae	Bo., Matt., Lon., Tab.	4	I	4	+	–
Seseli libanotis	Apiaceae	Matt., Tab.	2	I+A	4	–	+
Asarum europaeum	Aristolochiaceae	Bo., Fu., Matt., Tab.	4	I	0	–	–
Asparagus officininalis	Asparagaceae	Bo., Fu., Matt., Lon., Tab.	5	I	20	+	+
Artemisia abrotanum	Asteraceae	Fu., Matt., Tab.	3	I	15	+	+
Artemisia vulgaris	Asteraceae	Matt., Tab.	2	I+E			
Artemisia absinthium	Asteraceae	Bo., Matt., Tab.	3	I+E			
Helichrysum stoechas	Asteraceae	Matt., Tab.	2	I	1	+	–
Inula helenium	Asteraceae	Bo., Fu., Matt., Lon., Tab.	5	I+E	*		
Matricaria recutita	Asteraceae	Fu., Matt., Tab.	3	I+E	*		
Silybum marianum	Asteraceae	Bo., Matt., Lon.	3	I	9	+	+
Heliotropium europaeum	Boraginaceae	Matt., Lon.	2	I+E	2	–	–
Lithospermum officinale	Boraginaceae	Bo., Lon.	2	I	1	+	–
Symphytum officinale	Boraginaceae	Lon.	1	E	*		
Brassica oleracea	Brassicaceae	Bo., Fu., Matt., Lon., Tab.	5	I+E	0	–	–
Capparis spinosa	Capparaceae	Bo., Matt., Lon., Tab.	4	I	9	+	+
Bryonia dioica	Cucurbitaceae	Bo., Fu., Matt., Tab.	4	I+E	5	–	+
Citrullus colocynthis	Cucurbitaceae	Bo., Fu., Matt., Tab.	4	I+E	3		+
Juniperus communis	Cupressaceae	Fu., Matt., Tab.	3	I+E	3	+	+
Genista germanica	Fabaceae	Bo., Fu., Matt., Tab.	4	I+E	0	–	–
Centaurium erythraea	Gentianaceae	Bo., Fu., Matt., Lon., Tab.	5	I	1	–	+
Urginea maritima	Hyacinthaceae	Bo., Matt., Tab.	3	I	0	–	–
Hypericum perforatum	Hypericaceae	Bo., Fu., Matt., Lon., Tab.	5	I+E	7	–	–
Iris germanica	Iridaceae	Bo., Fu., Matt., Tab.	4	I+E	2	+	–
Calamintha nepeta	Lamiaceae	Fu., Matt.	2	I+E	0	–	–
Lavendula stoechas	Lamiaceae	Tab.	1	I	4	–	–
Rosmarinus officinalis	Lamiaceae	Fu., Matt., Lon.	3	I+E	9	+	+
Salvia aethiopis	Lamiaceae	Matt., Lon., Tab.	3	I+E	2	+	+
Salvia officinalis	Lamiaceae	Bo., Matt., Lon., Tab.	4	I+E	11		+
Stachys officinalis	Lamiaceae	Bo., Fu., Matt.	3	I+E	8	+	–
Teucrium chamaedrys	Lamiaceae	Bo., Fu., Matt., Tab.	4	I	1	–	–
Thymus vulgaris	Lamiaceae	Bo., Fu., Tab.	3	I+E	0	–	–
Lemna minor	Lemnaceae	Matt., Lon.	2	I+E	2	+	+
Asphodelus albus	Liliaceae	Matt.	1	I	2	–	–
Viscum album	Loranthaceae	Fu., Matt., Tab.	3	I+E	10	+	+
Myristica fragrans	Myristica ceae	Matt., Tab.	2	E	11	+	+
Papaver rhoeas	Papaveraceae	Bo., Fu., Matt., Lon., Tab.	5	I+E	0	–	–
Abies alba	Pinaceae	Matt., Tab.	2	I	0	–	–
Larix decidua	Pinaceae	Fu., Matt.	2	I	0	–	–
Plantago lanceolata	Plantaginaceae	Bo., Matt., Lon.	3	I+E	7	+	+
Avena sativa	Poaceae	Fu., Tab.	2	I+E	6	–	–
Hordeum vulgare	Poaceae	Bo., Fu., Matt., Lon., Tab.	5	I+E	2	+	–
Rheum rhabarbarum	Polygonaceae	Bo., Matt., Tab.	3	I+E	9	+	–
Primula veris, *Primula elatior*	Primulaceae	Fu., Matt., Lon., Tab.	4	I+E	0	–	–
Helleborus niger	Ranunculaceae	Bo., Fu., Matt.	3	I	0	–	–
Potentilla sp.	Rosaceae	Fu., Lon., Tab.	3	I+E	0	–	–
Rubia tinctorum	Rubiaceae	Bo., Fu., Matt.	3	I	0	–	–
Populus alba	Salicaceae	Bo., Matt., Tab.	3	I	0	–	–
Salix sp.	Salicaceae	Bo., Fu., Matt., Lon., Tab.	5	E	7	+	+
Saxifraga oppositifolia	Saxifragaceae	Tab.	1	I	0	–	–
Scrophularia nodosa	Scrophulariaceae	Bo., Lon., Tab.	3	I	18	+	+
Smilax sp.	Smilacaceae	Tab.	1	I	19	+	+
Physalis alkegengi	Solanaceae	Bo., Fu., Tab.	3	I	10	+	+
Daphne mezereum	Thymelaceae	Fu., Tab.	2	I+E	11	+	+
Urtica dioica	Urticaceae	Bo., Fu., Matt., Lon., Tab.	5	E	10	+	+
Verbena officinalis	Verbenaceae	Bo., Fu., Tab.	3	I+E	23		+

[a] The authors of the herbals who mention this plant.
[b] How many of the five herbals herbals mention athis plant Bo.: Bock (1577); Fu.: Fuchs (1543); Matt.: Matthiolus (1590); Lon.: Lonicerus (1770); Tab.: Tabernaemontanus (1687).
[c] Form of application described in the herbals: internal (I) or an external (A).
[d] Number of scientific literature citations sighted for this survey. Note: not all citations were used for the review.
[e] Avalability of *in vitro* data.
[f] Avalability of *in vivo* data.

Anethole, one of the components of the essential oil of *Foeniculum vulgare*, was a potent inhibitor (<1 mM) of NF-κB-activation (aspirin = 5 mM) in a number of *in vitro* studies (Chainy et al., 2000; Aggarwal and Shishodia, 2006; Kaileh et al., 2007). Choi and Hwang (2003) examined the antiphlogistic activity of a methanolic extract of *Foeniculi fructus in vivo*. In the three model systems carrageenan-induced paw oedema, arachidonic acid induced ear oedema and formaldehyde induced arthritis, significant inhibition was observed. Xanthin oxidase (XO) converts xanthin to uric acid, which in elevated levels leads to gout (Lin et al., 2002). Dew et al.

(2005) examined the *in vitro* activity of various medicinal plants used in traditional Chinese medicine (TCM), and Australia to treat gout for XO inhibiting properties. Here *Foeniculum vulgare* was in fact a weak promoter of XO.

The aerial parts and the roots of *Peucedanum ostruthium* (L.) Koch, Syn: *Imperatoria ostruthium* (L.) Koch (Masterwort) should be boiled in wine and drunk to heal joint pains. Painful limbs can also be rubbed in with a schnaps made *Peucedanum ostruthium*. Furthermore the roots, seeds, leaves and juice expel thick slime responsible for such pains (Bo, Fu, Matt., and Tab.).

The antiphlogistic activity of an ethanolic extract of the roots of *Peucedanum ostruthium* and the active coumarin ostruthin were shown in a carrageenan-induced rat paw oedema test system (Hiermann and Schantl, 1998).

A schnaps was made from the aerial parts and the roots of *Pimpinella saxifraga* (L.) (Burnet saxifrage). Taken with castoreum it should help against gout in ones limbs (Bo.; Matt.; Lon.; Tab.). Castoreum is a glandular secretion from the castor sacks of the male beaver (*Castor fiber*, Castoridae). The connection between the two drugs remains unclear to us.

In an *in vitro* study Tabanca et al. (2007) examined the antiphlogistic activity of the essential oil of *Pimpinella saxifraga* and some of the oils constituents. The essential oil inhibits NF-κB specifically with an IC_{50} of 45 μg/ml. Therefore 4-(2-propenyl)phenylangelate, 4-methoxy-2-(3-methyloxiranyl)phenylangelate, epoxypseudoisoeugenol-2-methylbutyrate had specific anti-NF-κB activity and may be responsible for the antiphlogistic activity.

Matt. and Tab. recommend making a juice called "Gummi Opapanacis" from the roots of *Seseli libanotis* (L.) Koch, to be drunk for joint pains. It can also be rubbed on painful hips and gout affected painful joints.

Seseli libanotis contains essential oil with trans-caryophyllene, spathulenol, (−)-caryophyllene oxide, euasarone and delta-cadinene (Ozturk and Ercisli, 2006), and the coumarins samidin, isosamidin, cis-and trans-khellactone (Glowniak, 1991). In TCM *Seseli mairei* Wolff is used for inflammatory ailments like rheumatism and colds (Hu et al., 1990). Selelin a coumarin from *Seseli indicum* had antiphlogistic activity in a TPA induced mouse ear oedema assay (Tandan et al., 1990; Garcia-Argaez et al., 2000). In a carrageenan induced paw oedema assay, *Seseli libanotis* was moderately active (Kupeli et al., 2006).

3.4. Aristolochiaceae

Asarum europaeum L. (Haselwort) is to be boiled in wine and drunk against gout and hip pains. The powdered roots drunk with met (honey wine) rid you of "tough slime" (Bo.; Fu.; Matt.; Tab.).

The essential oil of *Asarum europaeum* contains up to 50% of the toxic phenyl-propane asarone alongside mono- and sesquiterpenoids. Symptoms of intoxication with asarone include vomiting, sneezing, hallucinations, kidney damage, coma and respiratory paralysis. β-Asarone is thought to be carcinogenic (Hänsel et al., 1992).

3.5. Asparagaceae

Asparagus officinalis L. roots were boiled in water or wine and drunk against pains of the joints, hips and back and to cleanse the bladder of harmful substances, which cause gout of the feet (Bo.; Fu.; Matt.; Lon and Tab.).

In traditional Indian medicine the roots of *Asparagus racemosus* are used against rheumatism and inflammation (Goyal et al., 2003).

The roots of *Asparagus officinalis* contain flavonoids (Kartnig et al., 1985), oligosaccharides (Fukushi et al., 2000), amino acid derivatives (Kasai and Sakamura, 1981) and steroidal saponins (Shao et al., 1997). The latter are the main constituents found in a number of *Asparagus* species (Nwafor and Okwuasaba, 2002; Hayes et al., 2006a,b).

In vitro the isolated compound (+)-1-hexadecanoylglycerol had slight activity against COX-1 (100 μg/ml: 50% inhibition) and moderate activity against COX-2 (100 μg/ml: 67% inhibition), ferulic acid, 1,3-*O*-di-*p*-cumaroylglycerol and 1-*o*-feruloyl-3-*O*-*p*-cumaroylglycerol were weakly active against COX-1. *Trans*-resveratrol inhibited COX-1 and COX-2 to 100% at 100 μg/ml (Jang et al., 2004). Nwafor and Okwuasaba (2002) demonstrated *in vivo* that a methanolic extract of *Asparagus pubescens* inhibits albumin-induced rat paw oedema.

3.6. Asteraceae

Fu., Matt. and Tab. recommended boiling the seeds of *Artemisia abrotanum* L. (Southernwood) in wine or water (Fu. wrote that the flowers could also be used) and to drink the broth or rub it on painful joints.

According to Matt. and Tab. people suffering from gout of the feet should were to eat the *Artemisia vulgaris* L. roots (Mugwort). The flowers boiled up in white wine were to be applied to painful joint in soaked clothes (Tab.).

The genus *Artemisia* has over 300 species, making it one of the largest genera of the northern hemisphere. *Artemisia* species are in use for the treatment of malaria, hepatitis, cancer, inflammation, bacterial, viral and fungal infections (Tan et al., 1998).

In South America the leaves of *Artemisia copa* Phil. are macerated in alcohol and applied topically for rheumatic pains (Giberti, 1983). *Artemisia copa* contains flavonoids such as spinacetin, jaceosidin, axillarin, penduletin, tricin and chrysoeriol which were examined in an *in vitro* study. They all inhibited PGE_2-production (spinacetin, jaceosidin: IC_{50} = 5.1 μM). Furthermore jaceosidin reduced COX-2-activity with an IC_{50} of 2.8 μM (Moscatelli et al., 2005). The dichloromethane extract of *Artemisia copa* significantly inhibited TPA-induced mouse ear oedema by 84.8% at 1 mg/ear (indomethacin: 72.7%) but showed no effect in a carrageenan induced rat paw oedema assay (100 and 300 mg/kg). In previous studies luteolin, a flavonoid which is found in the plant, had been shown to have antitumour, antioxidative, antiphlogistic and analgetic effects (Block et al., 1998; Kotanidou et al., 2002).

The essential oil of *Artemisia caerulescens* L. which contains santonin, thujon, camphor, β-caryophyllene, borneol, nerol, α-terpineol etc. inhibited carrageenan-induced rat paw oedema (0.3 ml/kg = 43.4% inhibition; 1.0 ml/kg = 87.0% inhibition) comparable to lysine acetyl salicylate (75 mg/kg = 39.4% inhibition; 200 mg/kg = 79.4% inhibition) (Moràn et al., 1989).

In traditional Asian medicine *Artemisia asiatica* is commonly used for inflammations, cancer and microbial infections. Eupatalin a flavonoid found in *Artemisia asiatica* inhibits 5-LOX activity *in vitro* (Koshihara et al., 1983). Pre-treatment with 0.8 and 2.0 mg of DA-9601 – a standardised extract of *Artemisia asiatica* – led to a reduction of swelling in a TPA-induced mouse ear oedema assay (55 and 69% inhibition) (Seo et al., 2002).

A wine made with *Artemisia absinthium* L. (Absinthe wormwood) was used for gout of the feet. It was believed to internally cleanse the joints and prevent new harmful substances from going there. Painful joints were also to be rubbed in with *Artemisia absinthium* (Bo.; Matt.; Tab.).

Artemisia absinthium contains 0.2–1.5% essential oil with (+)-thujone, cis-epoxyocimen, *trans*-sabinyl acetate and chysanthenyl acetate, sesquiterpenes like α-bisabolol, β-curcumene as well as spathulenol sesquiterpene lactones like the dimeric guajanolide absinthiane, anabsinthine, artabsine, artabine and matricine and flavanol glycosides (Hiller and Melzig, 2006). In European folk medicine *Artemisia absinthium* was used for purgation, the inner cleansing of the body and is an ingredient of absinthe, a strong

alcoholic beverage, widely consumed in the 19th and early 20th century. Excessive consummation of the drink causes a mental and physical disorder called absinthism, which is attributed to thujone.

The leaves and flowers of *Helichrysum stoechas* Mill. soaked in wine were taken for hip- and back-pains and against gout of the feet (Matt. and Tab.).

Helichrysum stoechas contains the triterpenes ursolic- and oleanolic acid, uvaol and erythrodiol, the sterols β-sitosterol and stigmasterol, and the fatty acids linoleic-, palmitic-, linoleic and oleic acids and caffeic acid, the flavonoids apigenin, naringenin, kaempferol, luteolin, quercetin, helichrysin, apigenin-7-*O*-glucoside, kaempferol-3-*O*-glucoside, luteolin-7-*O*-glucoside, quercetin-3-*O*-glucoside (Garcia de Quesada et al., 1972).

Matt. recommended the roots and a wine made from *Inula helenium* L. (Elecampane) against gout and the juice of the plant to expel the slime and bile thought to be responsible for gout. All five of the authors describe cooking the leaves in wine and applying it to painful joints in a soaked cloth.

Helenalin, a sesquiterpene lactone found in some Asteraceae species like *Arnica* and *Inula*, has strong antiphlogistic activity *in vitro* and *in vivo*. It inhibits 5-LOX (Tornhamre et al., 2001) and NF-κB DNA-binding (Gertsch et al., 2003). At 10 μM helenalin reduced the mRNA of cytokines in Jurkat cells treated with PMA. It is a strong inhibitor of PMA-induced NF-κB p65 DNA-binding in PBM-cells with an IC_{50}-Wert < 5 μM, (Gertsch et al., 2003). Helenalin not only inhibits the activation of NF-κB but also directly inhibits activated NF-κB *in vitro* (Lyss et al., 1998). Helenalin irreversibly alkylates cysteine SH-moieties of the p65 subunit of NF-κB. Alkylation of p65 prevents DNA-binding of activated NF-κB. The reaction product of glutathione (GSH) with helenalin inhibits NF-κB activation entirely at 20 μM (Lyss et al., 1998).

Matricaria recutita L.; Syn. *Chamomilla recutita* L. (German chamomile) was used externally by rubbing its oil on painful joints with (Fu.; Matt.; Tab.). Tab. also recommended an internal use, whereby the flowers were soaked in wine over night and drunk against gout.

Nowadays infusions or aqueous dilutions of ethanolic extracts of *Matricaria recutita* are used externally for skin and mucosa infections and internally for spasms and inflammatory ailments of the digestive tract (Teuscher et al., 2004).

Matricaria recutita is officially listed in the Pharmacopoeia Europaea and is accredited with a multitude of beneficial properties like antiphlogistic, musculotropic, spasmolytic, promotion of wound-healing, deodorant, antibacterial, bacteriotoxin-inhibiting and enhancing of skin metabolism (Wichtl and Bisset, 1994). Over 120 compounds are known from *Matricaria recutita*. The essential oil (0.4–2%) consists of the terpenoids α-bisabolol and other bisaboloids, spathulenol and spiroether and the sesquiterpeneslacton matricin (prochamazulen). With an increase of temperature and/or in acidic milieu matricin is transformed to the deep blue artefact chamazulene. Further constituents are the flavonoids apigenin, quercetin, patuletin, luteolin and their glycosides, the coumarins herniarin and umbelliferone, polysaccharides, lipids and sterols (Hitziger et al., 2003).

In a number of assays (carrageenan-induced rat paw oedema, croton oil-induced mouse ear oedema) it has antiphlogistic activities comparable to acetyl salicylic acid (ASS). *In vitro* the flavonoid apigenin inhibits IL-1α induced PG synthesis and TNF_{α} induced IL-6 and IL-8 production (McKay and Blumberg, 2006), and reduces the peroxidation of arachidonic acid (Ammon et al., 1996). *In vivo* α-bisabolol reduces carrageenan induced paw oedema and adjuvans arthritis and is anti-ulcerogenic. It inhibits 5-LOX *in vitro* (Ammon et al., 1996).

Bo., Matt. and Lon. recommend cooking the roots of *Silybum marianum* L. (Blessed milk thistle) in water or wine and drinking it to ease sore joints.

Silybum marianum is used for chronic inflammatory liver diseases, liver cirrhoses and as a complimentary treatment in cases of toxic liver injury for dyspeptic complaints. Silymarin, a mixture of flavanolignans consisting of silybin, silydanin and silychristin (Leng-Peschlow, 1996) found in the blessed milk thistle inhibits a number of proinflammatory factors (e.g. TNF_{α}) and the activation of NF-κB (for example: TNF_{α}-induced NF-κB-activation) (Baeuerle and Baichwal, 1997; Zi et al., 1997; Manna et al., 1999; Khanna et al., 2007). *In vitro* silymarin inhibits IL-1β-induction and PGE_2-production (Kang et al., 2003). Silymarin has an inhibiting effect, in higher doses however an enhancing effect on the expression TNF_{α}, IL-1β and IL-6 *in vivo* (Johnson et al., 2003). It reduced carrageenan-induced rat paw oedema and xylen-induced mouse ear oedema to a similar extent as indomethacin did (Manna et al., 1999).

3.7. Boraginaceae

An aqueous extract of *Heliotropium europaeum* L. (European heliotrope) was valued for its laxative effects, which cleansed from within (Matt. and Lon.). The leaves of the plant were to be used externally for gout-ridden limbs (Matt.; Lon.).

The drastic purgative effects this plant has have not escaped scientist's attention either (Al-Qura'n, 2005). The leaves contain pyrrolizidine-alkaloids, a alkaloid class mainly found in Asteraceae and Boraginaceae species and known to be hepatotoxic and carcinogenic. Furthermore, *Heliotropium europaeum* contains the alkaloids europine, heliotrine, supinine, heleurine, lasiocarpine and 7-angelylheliotrine (Tosun and Tamer, 2004).

Bo. and Lon. recommended drinking pulverised stone seed (*Lithospermum officinale* L.) in wine to cleanse the bladder of harmful substances which caused gout. The main constituents from *Lithospermum officinale* are phenolic acids, tannins and naphtoquinones (Trouillas et al., 2002). *In vitro* a water–ethanol extract of *Lithospermum officinale* was antiphlogistic (IC_{50} was 1.5 mg/ml) which was presumed to be due to inhibition of LOX by anti oxidative phenolics (Trouillas et al., 2002).

Symphytum officinale L. was applied externally to painfull joints (Lon.).

Symphytum officinale has long been used as a medicinal herb. It contains allantoin and rosmarinic acid (Andres et al., 1989), mucopolysaccherides and pyrrolizidin alkaloids. It has antiphlogistic and analgetic activities (Koll et al., 2004) and the European pharmacopoeia commission E remommends the external use of *Symphyti radix* for bruises, swellings and sprains.

In a randomised placebo controlled double blinded study 140 patients with ankle distortions were given a comfrey ointment. The reduction of the swelling was significantly over that of the control group ($n = 60$). Also the subjectively felt pain was reduced significantly (Koll et al., 2004). The usefulness of *Symphytum officinale* for ailments of the musculoskeletal system has been shown in a number of clinical studies (Hess, 1991; Schmidtke-Schrezenmeier, 1992).

3.8. Brassicaceae

Various different sorts of cabbage (*Brassica oleracea* L.) rid the body of harmful substances when eaten or when the juice is drunk. Painful joints were to be wrapped in cloths soaked in cabbage juice. Limbs with polyarthritis and gout should be rubbed with a mixture of cabbage, flower and fenugreek (*Trigonella foenum-graecum* L. Fabaceae) (Bu., Fu., Matt., Lon., Tab.).

Cabbage contains glucosinolates, such as glucobrassicin and its bioactive hydrolysis product indol-3-carbinol, gluconasturtin, glucoraphanin, progoitrin, sinigrin und glucotropeolin.

3.9. Capparaceae

The bark of *Capparis spinosa* L. (Caper bush) was cooked in Met (honey wine) and drunk to expel the thick slime that causes gout, gout of the feet, hip and other pains in the joints. Juice from *Capparis spinosa* was used as an enema to internally cleanse the body to help against hip pains (Bo.; Matt.; Tab.; Lon.).

In traditional Saudi Arabian medicine *Capparis spinosa* is used in the treatment of rheumatism, arthritis and gout. A number of constituents have been isolated from *Capparis spinosa* including alkaloids, lipids, polyphenols, flavonoids, indoles and aliphatic glucosinolates (Rodrigo et al., 1992; Sharaf et al., 2000).

In an *in vitro* study a lyophilised extract of *Capparis spinosa* inhibited PGE_2-production between 10 and 51% in the concentrations 10, 100 and 200 μg/ml (Panico et al., 2005). An aqueous extract of *Capparis spinosa* significantly inhibited carrageenan-induced rat paw oedema assay (Ageel et al., 1986).

Al-Said et al. (1988) isolated the polyphenols cappaprenol 12, 13 and 14 from *Capparis spinosa* of which cappaprenol 13 inhibited carrageenan-induced rat paw oedema to 44% nearly as potently as the reference oxyphenbutazone.

3.10. Cucurbitaceae

The roots of *Bryonia dioica* Jacq. (Bryony) were mixed with olive oil and lard (pig's fat) and applied to the painful joints. Furthermore a schnaps was be made from the roots to be applied externally for arthritis (Bo.; Fu.; Matt.; Tab.).

Bryonia dioica contains sterols and triterpenes and their glycosides (Akihisa et al., 1994, 1996). The six triterpene-glycosides, bryonioside B, C, E and G, cabenoside D and bryoamaride inhibited TPA-induced mouse ear oedema. The antiphlogistic activity of these triterpene glycosides (ID_{50} = 0.2–0.7 mg/ear) was stronger than the reference quercetin (ID_{50} = 1.6 mg/ear) and comparable to indomethacin (ID_{50} = 0.3 mg/ear (Ukiya et al., 2002)).

The marrow of the colocynth fruit *Citrullus colocynthis* L. inwardly cleansed the body and expelled though slime, hereby relieving pains from gout. An enema from the marrow was used to relieve pains of the hips. This medicine was only to be taken by strong and able people. Not by children and pregnant women as *Citrullus colocynthis* is a drastic laxative (Bo.; Fu.; Matt.; Tab.). Three antioxidative flavone-glycosides isosaponarin, isovitexin and isoorientin were isolated from *Citrullus colocynthis* (Delazar et al., 2006). In a carrageenan induced rat paw oedema assay an extract of *Citrullus colocynthis* showed antiphlogistic activity (Wasfi et al., 1995).

3.11. Cupressaceae

Matt. recommended cooking juniper berries *Juniperus communis* L. (Common juniper) in wine, whereas Fu. advises eating the berries to expel slime. Both of them mention rubbing the oil on sore joints, and Matt. also explained that having a bath in juniper-wood water would ease pains.

Over 100 substances, including 64 sesquiterpene lactones have been isolated from juniper berries. In an *in vitro* study Tunón et al. (1995) showed that *Juniperus communis* essential oil had a moderate inhibitory effect (55% at 0.2 mg/ml) on PG-production. An ethanolic extract was active in a rat paw oedema assay (Mascolo et al., 1987).

3.12. Fabaceae

The seeds of *Genista germanica* L. (Broom) expelled harmful substances which caused gout. Vinegar into which the plant had been placed for several days was be drunk against pains of the hips (Bo.; Fu.; Matt.; Tab.).

The leaves and the seeds of *Genista germanica* contain the highly toxic alkaloid sparteine (0.2–0.3%), scoparine, essential oil and tannins. The seeds also contain the toxic alkaloid cytisine (Hiller and Melzig, 2006).

3.13. Gentianaceae

Aerial parts of centauries (*Centaurium erythraea* C.G. Rafn.) were cooked in water or wine and drunk to remove the bile and slime responsible for pains in the joints. The decoction was also applied as a clyster against hip pains (Fu.; Bo.; Matt.; Lon.; Tab.). Bo. describes how to make tablets out of powdered centauries for the treatment of gout and joint pains.

In European folk medicine *Centaureum erythraea* is used to treat inflammatory ailments. Applied topically in an air pouch granuloma assay the aqueous extract in 2.5 and 5% extract creams inhibited the inflammation by 19 and 42%. In the *Mycobacterium* adjuvans polyarthritis model there was a clear reduction of the inflammation and of weight loss in higher test concentrations from 50 to 500 mg/kg (Berkan et al., 1991).

3.14. Hyacinthaceae

A vinegar called "Oxymel Scilliticum" was made from sea onion *Urginea maritima* (L.) Baker, Syn: *Scilla maritima* L. which when drunk would – just like all the other bile and slime removers – help against joint pains (Bo.; Matt.; Tab.).

Urginea maritima contains 1–3% cardiac glycosides (bufadienolides), such as glucoscillarene A, proscillaridine A, scillarene A, scilliglaucoside and scilliphaeoside, flavonoids and polysaccharides. Standardised preparations of *Urginea maritima* are used for mild forms of heart insufficiency and bad kidney performance (Hänsel et al., 1994).

3.15. Hypericaceae

The seeds of *Hypericum perforatum* L. (St. John's wort) were to be cooked and the broth drunk for 40 days to ease pains of the hip (Bo.; Fu.; Matt.; Lon.; Tab.). Lon. recommends drinking wine containing the dried and pulverised herb against gout in the feet.

Hypericum perforatum is an old medicinal herb with wound healing, anti rheumatic, diuretic and antidepressant activities. It contains hypericin, a naphthodianthrone with antidepressant, antiviral and antineoplastic activities (Lavie et al., 1995) that has been suggested for the treatment of AIDS/HIV and inflammatory diseases (Fox et al., 1998).

Hypericin significantly reduced IL-12-production was *in vitro* (IC_{50} = 1.45 μg/ml) possibly by reduction of NF-κB-activation (Kang et al., 2001).

A water/ethanol extract of *Hypericum perforatum* inhibited 5-LOX *in vitro* (Herold et al., 2003). In an *in vivo* study a *Hypericum perforatum* extract inhibited carrageenan- and PGE_1-induced inflammation in and leukocyte infiltration (Shipochliev et al., 1981). Mascolo et al. (1987), on the contrary, found an ethanolic extract to be inactive.

3.16. Iridaceae

Fu., Bo., Matt. and Tab. recommend boiling the roots of iris (*Iris germanica* L.) in water and applying as an enema or rubbing the oil on arthritic limbs.

Atta-ur-Rahman et al. (2003) isolated nine isoflavonoids from *Iris germanica* and tested their antiphlogistic activity in an *in vitro* assay based on the reduction of the tetrazolium salt WST1 in the presence of activated human neutrophiles, which can be measured spectrophhotometrically. The 50% inhibition val-

ues ranged 51–487.08 μM (positive controls: ASS IC_{50} = 67.74 μM, indomethacin IC_{50} = 81.36 μM).

3.17. Lamiaceae

Matt. advised boiling *Calamintha nepeta* L. and drinking the broth against gout and tough slime. Fu. recommends an external application of the leaves against hip pains. *Calamintha nepeta* contains approximately 0.35% essential oil containing pulegone and other ketones.

Matt. and Tab. report a "Syrup de Stoechade" made from the flowers of *Lavandula stoechas* L. against all the "sicknesses of the nerves" that are caused by the cold. This also included gout.

Lavendula stoechas is used in folk medicine on Sardinia for its antispasmodic, sedative, diuretic and antirheumatic properties (Atzei, 2003). *Lavendula stoechas* contains triterpenes, steroids (Topcu et al., 2001) and essential oil with fenchone and camphor (Angioni et al., 2006). In Iranian folk medicine *Lavandula angustifolia* Mill. extracts are used as remedies for the treatment of various inflammatory diseases. A water/ethanol extract, a polyphenolic fraction and the essential oil of the leaves of *Lavandula angustifolia* were tested in formalin- and acetic acid-induced writhing tests in mice and carrageenan induced oedema test in rats (Hajhashemi et al., 2003). At 400–1600 mg/kg the extract inhibited only the second phase of formalin test. The polyphenolic fraction (800 and 1600 mg/kg, p.o.) and essential oil (100 and 200 mg/kg, p.o.) suppressed both phases. In acetic acid-induced writhing test the polyphenolic fraction (400 and 800 mg/kg, p.o.) and the essential oil (100 and 200 mg/kg, p.o.) reduced the number of abdominal constrictions. Essential oil at a dose of 200 mg/kg also inhibited carrageenan-induced paw oedema.

Rosemary (*Rosmarinus officinalis* L.) boiled in water or wine was drunk against cold thick gout causing slime. The essential oil was used externally against gout (Fu., Matt. and Lon.).

In Europe rosemary has long been valued for its analgetic and antiphlogistic effects (Al-Sereiti et al., 1999). Just like many other Lamiaceae it contains rosmarinic acid (Lo et al., 2002), which inhibits COX and LOX *in vitro* (Sahu et al., 1999; Kelm et al., 2000).

In a collagen-induced arthritis model in mice – a test system said to model human rheumatoid arthritis (RA) – repeated uptake of rosmarinic acid eases arthritis-like symptoms significantly (Youn et al., 2003). Rosmarinic acid also induces apoptosis of activated T-cells, which play an important role in RA (Hur et al., 2007).

In an *in vitro* study Tripp et al. (2005) showed that the standardised extract Meta050 – a mixture of Iso_{α}-acids from hops (*Humulus lupulus* L. (Cannabaceae)), rosemary extract and oleanolic acid – inhibits PGE_2-production. In an eight week long observational study with 54 participants with a rheumatic disorder subjectively felt pain was reduced by 40–50% (Lukaczer et al., 2005).

A beverage from roots of *Salvia aethiopis* L. helped against thick slime, and herby cured sore hips (Matt., Tab. and Lon.).

The roots of *Salvia aethiopis* contain aethiopinon, an O-naphtoquinone-diterpene, which inhibits 5-LO *in vivo* (Hernández-Pérez et al., 1995). The antiphlogistic activity has also been shown *in vivo*: aethiopinon reduced leukocyte accumulation and LTB_4 levels in a zymosan-injected air pouch-model and inhibited 5-LOX after topical application in an arachidonic acid induced ear oedema model (Benrezzouk et al., 2001).

Salvia officinalis L. (Common sage) was boiled in wine to be drunk rubbed on limbs with gout (Bo.; Matt.; Lon.; Tab.). Possibly this recipe also meant *Salvia pratensis* L. (Meadow sage).

The essential oil had no antiphlogistic activity in a croton oil-induced mouse ear oedema assay. The methanolic extract was also practically inactive. The chloroform extract, however, did show a clear activity. Ursolic acid was isolated and it had an activity comparable to oleanolic acid and indomethacin (ursolic acid: 0.4 μmol/cm^2 = 84% inhibition; oleanolic acid: 1 μmol/cm^2 = 74% inhibition; indomethacin: 0.50 μmol/cm^2 = 77% inhibition) (Liu, 1995).

A broth made from the boiled roots of *Stachys officinalis* L., Syn: *Betonica officinalis* L. (Purple betony), but also the flowers in sugar were thought to ease polyarthritis, gout of the feet, hip pains and lameness of the limbs (Bo.; Fu.; Matt.).

Salvia officinalis contains flavonoids, phenolic acids, phenylethanoid glycosides, iridoid glycosides, diterpenes and essential oils (0.5%) with isocaryophyllene and β-caryophyllene as the main components (Jeker et al., 1989).

The aerial parts of *Teucrium chamaedrys* L. (Wall germander) were boiled in wine and this concoction was taken for 60 days 3 h before meals on an empty stomach. The patienta wishing cure of his gout of the feet and hip pains with this remedy were also to avoid eating sour and salty foods (Tab.).

Teurium chamaedrys contains essential oil (0.07%) with β-caryophyllene and humulene, iridoid glycosides (acetyl harpagide and harpagide), diterpenes (dihydroteugin and marrubiin), flavonoids and phenylpropanes such as the phenylpropanoid glycoside teucrioside.

In 1986 in France an officially approved germander preparation caused liver damage, possibly due to hepatotoxic furano-diterpenoids (Stickel et al., 2001).

Thyme (*Thymus vulgaris* L.) was to be taken in vinegar to expel that harmful slime, and thus help cure polyarthritis and gout. It could also be mixed with barley malt and laid on painful joints (Bo., Fu. and Tab.).

Thymus vulgaris contains 1–2.5% essential oil with thymol, carvacrol, *p*-cymene, γ-terpinene, thymolmethylether, furthermore flavones like apigenin, luteolin, methoxylated and glycosylated flavones, tannins, phenolic acids and triterpenes.

3.18. Lemnaceae

Even the miniscule duckweed (*Lemna minor* L.) was used to treat rheumatic disorders. In the month of June a schnaps was distilled, which when consumed in large quantities soothed gout of the feet (Lon.).

Lemna minor contains the pectin polysaccharide lemnan which enhances ovalbumin-induced mouse paw oedema (Popov et al., 2006) and stimulates neutrophiles and macrophages (Ovodova et al., 2000). It is therefore actually proinflammatory. A pectin will, however, hardly be in the distillate and little is known of the rest of duckweeds phytochemistry.

3.19. Liliaceae

Asphodel *Asphodelus albus* Mill. roots boiled in wine should help against gout of the feet (Matt.). The roots contain anthranoids/anthraquinones, which are laxatives (Popovic et al., 2004; Utrilla et al., 1989). Anthranoids such as emodine from *Rhamnus* species (Rhamnaceae) have been described as anti-inflammatory in a carrageenan induced rat paw oedema (Goel et al., 1991).

3.20. Loranthaceae

Mistletoe (*Viscum album* L.) was extracted a couple of days in wine and then a strong schnaps was distilled. The schnaps should be drunk to expel the nasty old slime that was considered to cause gout, or just rubbed on the affected joints (Fu., Matt., Tab.).

Mistletoe is hypotensive, vasodilating, sedative, diuretic, immunmodulatory, antiphlogistic, is used to treat hypertension and arteriosclerosis, for peri-arthritis, spondylitis and arthritis as well as for head aches. In Europe mistletoe preparations are used in adjuvant cancer therapy (Wichtl and Bisset, 1994).

Aqueous extracts contain low molecular peptides like lectins and viscotoxines which induce the release of proinflammatory cytokines, whereas ethanolic extracts with their flavonoids, phenolic acids, phenylpropanoids and lignans have antiphlogistic activities (Mannel et al., 1991).

Orhan et al. (2006) examined the *in vivo* antiphlogistic activity of a mistletoe ethyl acetate extract and some purified flavonones and chalcones. The extract inhibited carrageenan-induced rat paw oedema 24.7–37.2% at inhibition at 10 mg/kg. The chalcon had a similar activity (30.7–33.6% inhibition) and the three flavonones had a weak but significant antiphlogistic activity (15.1–21.3%; 8.0–25.2%; 13.3–31.5% inhibition at 10 mg/kg).

3.21. Myristicaceae

A resin was obtained from the nutmeg bark (*Myristica fragrans* Houtt.) which was used externally to treat polyarthritis and gout of the feet (Matt., Tab.).

In Indonesian folk medicine the arillus of nutmegs is used for rheumatism (Perry, 1980). The nuts with the arillus contain myristicin and eugenol.

Ozaki et al. (1989) examined the antiphlogistic activity of a 70% methanolic extract of *Myristica fragrans in vivo* using a carrageenan-induced rat paw oedema. The extract inhibited the oedema at 1.5 g/kg (indomethacin 10 mg/kg), and the activity was traced to myristicin which inhibited at 0.17 g/kg. The authors just want to note here that anybody who eats 1.5 g/kg of nutmeg, let alone a concentrated extract is going to die a very painful death. Eugenol is antiphlogistic and antioxidative (Ko et al., 1995) and alongside its derivatives inhibits various mediators of inflammation, including LPS-stimulated NF-κB-activation and COX-expression (Kim et al., 2003; Murakami et al., 2005).

3.22. Papaveraceae

Bo., Matt. and Tab. recommend boiling poppy roots (*Papaver rhoeas* L.) and drinking the brew against pains of the hips (Fu.). Lon. suggested rubbing poppy juice on affected limbs. *Papaver rhoeas* contains 0.11–0.12% alkaloids like rhoeadine (Hiller and Melzig, 2006).

3.23. Pinaceae

Sap from the silver fir (*Abies alba* L.) of was used for gout of the feet and hip pains (Matt.) Tab. recommended distilling a schnaps from the sap.

Sap from *Abies alba* once known as “Strassburger Terpentin”, contains essential oil, resene, succinic acid, bitter principles and resin acid.

A schnaps was also made from the sap of European larch (*Larix decidua* Mill.) which, when drunk, expelled old slime and helped sore joints (Fu.; Matt.).

Larix decidua contains essential oil (15%) with α-pinene as the main constituent and borneol, dipentene and guajacol, acids like laricinolic acid, laricorosene and larixylacetate and abietic acid (Hiller and Melzig, 2006).

3.24. Plantaginaceae

The juice of *Plantago lanceolata* L. (Ribwort plantain) and *Plantago major* L. were be drunk with wine or honey against gout (Lon.). *Plantago lanceolata* leaves crushed with salt were to be placed on arthritic limbs (Bo.; Matt.; Lon.).

Nowadays *Plantago lanceolata* is used for catharses of the upper respiratory tract and ailments in mouth and throat. Externally it is used for skin diseases. *Plantago lanceolata* contains the phenylethanoids acteoside, cistanoside F, lavandulifolioside, plantamajoside and Iisoacetoside flavonoids like apigenin, quercetin, plantaginin and aucubin the iridoid glucoside catalpol (Murai et al., 1995). Extracts from *Plantago lanceolata* and *Plantago major* were antiphlogistic in carrageenan- and PGE_1-induced inflammations in rats (Shipochliev et al., 1981). Acteoside, the main phenylethanoid from *Plantago lanceolata* inhibits arachidonic acid induced mouse ear oedema (Murai et al., 1995). *In vitro Plantago lanceolata* extract reduced NO-production significantly and was comparable to dexamethason and indomethacin. The same extract had no significant effect on COX-2 or PGE_2 (Vigo et al., 2005).

3.25. Poaceae

Eating oats (*Avena sativa* L.) rids you of the thick slime that causes polyarthritis and gout of the feet (Tab.). Oats mixed with vinegar should be placed on gout of the foot (Fu.; Tab.). *Avena sativa* is used in European folk medicine for rheumatism, gout, liver- and skin diseases (Schneider, 1985). It contains saponins, C-glycosyl flavones, flavonoid-O-glycosides (Chopin et al., 1977). Wenzig et al. (2005) isolated three flavano -lignans salcolin A and B and neohydnocarpin.

Barley flour (*Hordeum vulgare* L.) can be used externally for gout and rheumatism by putting on joints like a plaster (Bo.; Fu.; Matt.; Lon.; Tab.).

3.26. Polygonaceae

Rheum rhabarbarum L. (Rhubarb) expelled thick slime and helped against gout (Bo.; Matt.; Tab.).

In rhubarb we find minerals, vitamins, nicotinamide, carotinoids, oxalates, malic- and citric acid. Many studies have been done on *Rheum palmatum* L. an important plant in TCM. The main constituents from *Rheum palmatum* are antraquinone-derivatives like aloe-emodin, chrysophanol, emodin, physcion, rhein and sennoside A and B. These are not found in *Rheum barbarum* which is why no further attention will be paid to this common TCM plant here.

3.27. Primulaceae

Fu. called primulas “Arthritica” which indicates that Primula species were plants widely known as plants used against gout. They can be prepared as a schnaps or wine, the flowers can be eaten with sugar or crushed to be laid on painful joints (Fu.; Matt.; Lon.; Tab.). Nowadays *Primula* species like *Primula veris* L. (Cow slip) and *Primula elatior* L. (Oxlip) are used for catharses of the upper respiratory tract (Hiller and Melzig, 2006). They are found in cough teas, liquid- and dry extracts and syrups (Teuscher et al., 2004). Rhizomes and flowers are valued for their expectorant, anticonvulsant and relaxant activities. In European folk medicine *Primula* species are used for bronchitis, cough, migraine and sleeping disorders. The flowers contain flavonoids like apigenin and luteolin, kaempferol and quercetin glycosides, saponins, carotinoids and small quantities of essential oils. The rhizomes contain 4–10% triterpene saponins, phenol glycosides like primverin and primulaverin and some essential oil.

3.28. Ranunculaceae

Helleborus niger L. (Hellebore) expelled thick slime and help sore joints (Bo.; Fu.; Matt.). *Helleborus niger* contains saponins and protoanemonin, a toxic lactone of hydroxy-penta-2,4-dienic acid, and the cardiac glycoside helleborin and the steroidsaponin hellebrin. All parts of the plant are toxic. In European folk medicine *Helleborus niger* is used as an emetic and laxant and it used to be used in sneezing powders.

3.29. Rosaceae

The roots of *Potentilla* sp. were cooked and the broth drunk to soothe polyarthritis and gout of the feet. Wine with potentilla was said to help against polyarthritis, gout of the feet and pains of the feet hips and knees (Fu.; Lon.; Tab.).

Potentilla species are used as astringent, for mild dysmenorrhoea complaints, and in supporting therapy for severe diarrhoea and for infections of the mouth and throat (Hiller and Melzig, 2006). *Potentilla* species contain flavonoids, phenolic acids like *p*-cumaric-, ferulic- and caffeic acid, ellagitannins and vitamin C.

3.30. Rubiaceae

Roots of *Rubia tinctorum* L. (Madder) were cooked in met (honey wine) to soothe joint pains and strengthen lame and weak bones (Bo.; Fu.; Matt.). *Rubia tinctorum* contains 2–4% di- and trihydroxyanthraquinone derivatives of the rubiadin-type, anthracene derivatives like alizarin, ruberythrinic acid derivatives like lucidin, pseudopurpurin, purpurin, rubiadin and glucoside and primveroside derivatives thereof as well as rubi chlor, citric and other plant acids, tannins, pectins, sugars proteins and fatty oils (Hiller and Melzig, 2006).

3.31. Salicaceae

Bo., Matt. and Tab. recommended drinking pulverised bark of *Populus alba* L. (White poplar) to soothe hip pains and joint pains in general. In European folk medicine *Populus alba* has been used for polyarthritis and was part of *Unguentum populi*, an ointment used for gout and rheumatism (Hiller and Melzig, 2006). Poplars contain the phenolic glycosides salicin and populin. For studies on salicin please refer to the next section on *Salix* spp.

The bark and the leaves of *Salix* sp. (Willow) was cooked in water and the broth applied to painful joint in a cloth (Bo.; Fu.; Matt.; Lon.; Tab.).

Willow bark extracts are a remedy approved by the European Pharmacopoeia commission for treating fever, rheumatic disorders and head aches. Salicin and related glycosides are responsible for this activity (Schmid et al., 2001).

A study on the pharmacokinetics of salicin after oral intake of 240 mg ($n + 10$) showed that salicylic acid was the main metabolite in the serum and urine with a concentration comparable to 87 mg of ASS (Benedek et al., 1995; Schmid et al., 2001). The standardised willow bark extract STW 33I was tested in the carrageenan-induced rat paw oedema- and in the "adjuvans arthritis"-model where STW 33I was at least as active as ASS (Khayyal et al., 2005).

In a randomised double blinded control study with 127 participants with AO (43 received willow bark extract, 43 diclofenac, 41 placebo for 6 weeks) the improvements in pain, stiffness and quality of life after intake of willow bark extracts were hardly better than the placebo. Also with the 26 persons with RA took part in the study (13 willow bark extract, 13 placebo) there were no significant improvements over the placebo (Biegert et al., 2004). In a number of *in vitro* and *ex vivo* studies, on the other hand, willow bark extracts have indeed been shown to be antiphlogistic and to inhibit COX-2-induced PGE_2-release and the release of TNF_α and IL-1β (Fiebich and Chrubasik, 2004). The lack of activities *in vivo* may have been due to test concentration being to low to show the analgetic and antirheumatic effects (Wagner et al., 2003).

3.32. Saxifragaceae

For 40 days a decoction of the roots of *Saxifraga oppositifolia* L. (Purple Saxifrage) was taken to treat polyarthritis and gout of the feet (Tab.) Purple saxifrage contains tannins and bitter principles (Hiller and Melzig, 2006).

3.33. Scrophulariaceae

The seeds of figwort (*Scrophularia nodosa* L.) together with pepper (*Piper nigrum* L., Piperaceae), myrrh (the resin of *Commiphora myrrha* Arn., Burseraceae) and wine are to be drunk to soothe pains in the hips (Bo.; Lon.; Tab.).

In TCM a number of *Scrophularia* species are used to treat inflammations (Kajimoto et al., 1989). The iridoid glycosides aucubin, harpagid, 6-rhamnosyl-catalpol, harpagoside and harpagidacetate were isolated from *Scrophularia nodosa* (Weinges and von der Eltz, 1978).

The saponins verbascosaponin and verbascosaponin A, and the iridoids scrovalentinoside and scropolioside A were isolated from *Scrophularia auriculata* and tested in a number of *in vivo* inflammatory models. Verbascosaponin showed the strongest inhibition of carrageenan induced rat paw oedema, inhibiting 52% after 1 h (100 mg/kg) (reference drug; indomethacin = 34% inhibition at 7 mg/kg), after that the activity decreased. The inhibition of 33% after 3 h by scropolioside (100 mg/kg) was comparable to indomethacin. TPA-induced ear oedema was inhibited by both saponins (verbascosaponin: $ID_{50} = 0.18$ μM/ear; verbascosaponin A: $ID_{50} = 0.32$ μM/ear; indomethacin: $ID_{50} = 0.35$ μM/ear). Both the iridoids had weaker, yet significant activities: scrovalentinoside: 52% inhibition; scropolioside A: 47% inhibition (0.5 mg/ear). After multiple topical applications of TPA (a model for chronic inflammation) the oedema was still significantly inhibited (0.5 mg/ear) by verbascosaponin A to 67%, verbascosaponin 58%, scrovalentinoside 47% and scropolioside A to 38% inhibition, respectively. Verbascosaponin A, scrovalentinoside and scropolioside A were applied 16 h prior to ethylphenylpropiolate-application and they reduced the oedema by 67, 56 and 37% respectively. When applied simultaneously with ethylphenylpropiolate this activity was not seen, an observation that has also been seen with the corticosteroid dexamethason: 16 h prior – 82% inhibition; 2 h prior – 20% inhibition. Neither the iridoids nor the saponins inhibited arachidonic acid induced oedema (Giner et al., 2000).

The iridoid scrovalentinoside from *Scrophularia auriculata* L. was studied *in vitro*. The production of the pro-inflammatory cytokines, PGE_2, LTB_4 and NO was reduced. Scrovalentinoside inhibited the expression von iNOS, but did not influence levels of already available NO (Bas et al., 2007). Seven iridoid glycosides were isolated from *Scrophularia scorodonia* and identified as bartioside, aucubin, harpagid, harpagoside, 8-acetylharpagosid, scorodioside and scropolioside B. Bermejo et al. (2000) tested their effects on PGE_2- and LTC_4 release. Only aucubin showed a slight activity in the LTC_4-assay ($IC_{50} = 72$ μM, NDGA $IC_{50} = 1.5$ μM). The five phenylpropanoidglycosides, angoroside A, C and D, acteoside and isoacteoside were isolated from *Scrophularia scorodonia* L., and tested for antiphlogistic activities. None inhibited 5-LOX, but angoroside A and D, acteosid and isoacteoside nearly completely inhibited LPS-induced PGE_2 release at 100 μM. Also at 100 μM all five phenylpropanoid glycosides inhibited NO production, and- with the exception of angoroside- also TNF_α.

3.34. Smilacaceae

The roots of *Smilax* sp. (Sarsaparilla) were used for gout of the feet and to expel slime (Tab.).

There are about 350 *Smilax* species in tropical and temperate climatic zones, mostly in East Asia and North America. In TCM some *Smilax* species are used for their antiphlogistic, anti-carcinogenic and analgetic activities. *Smilax sarsaparilla* L. is used in Traditional Saudi Arabian medicine for rheumatism, arthritis, gout and other

inflammatory disease. *Smilax china* L. is used for the treatment of rheumatoid arthritis, gout and other inflammatory ailments. *Smilax china* L. contains saponins like smilaxin, prosapogenin A of dioscin, gracillin, dioscin, pseudoprotodioscin, methygracillin and methylprotodioscin (Sashida et al., 1992).

Shao et al. (2006) examined the COX-2 inhibiting effects of nine steroidal saponins from *Smilax* species. At 10^{-5} M all of them showed significant inhibiting activity: between 59 and 82%. An aqueous extract from *Smilax china*, which contained saponins, flavonoids and other water soluble constituents, inhibited albumin-induced rat paw oedema at very high concentrations of 1000–2000 mg/kg. The extract reduced PGE_2-production, by inhibiting COX-2-activity with 81.25% inhibition at 100 μg/ml (indomethacin: 69.07% at 0.4 μg/ml (Shu et al., 2006). In an *in vivo* study Jiang and Xu (2003) showed the antiphlogistic effects of an aqueous extract of *Smilax glabra* Roxb. rhizomes in a adjuvans arthritis model. The production of IL-1, TNF, NO was significantly reduced at 400 or 800 mg/kg. Ageel et al. (1989) reported that after oral application of 500 mg/kg of ethanolic *Smilax sarsaparilla* extract carrageenan-induced rat paw oedema was reduced by 25%.

3.35. Solanaceae

Fruits of *Physalis alkekengi* L. (Chinese lanterns) were used to drive out with ones urine those harmful substances that cause gout of the feet (Bo.; Fu.; Tab.).

Various *Physalis* species have been used in folk medicine around the world for diseases such as malaria, asthma, hepatitis, dermatitis and rheumatism. *Physalis* species are anti-carcinogenic, anti-mycobacterial, antipyretic, immune-modulatory and diuretic (Perry, 1980; Lin et al., 1992).

The seco-iridoid physalin, from *Physalis angulata* L. is immune-modulatory (Soares et al., 2003). Choi and Hwang (2003) examined the antiphlogistic action of *Physalis angulata in vivo* using various inflammation models. The inhibition in the carrageenan-induced rat paw oedema by the methanolic extract of *Physalis angulata* was 68% at 200 mg/kg (Choi and Hwang, 2003). The inhibition of arachidonic acid induced ear oedema was 41% at 200 mg/kg.

The supercritical CO_2-extract with 5% ethanol of *Physalis peruviana* was stronger than other extracts from the same plant and it had the highest concentration of flavonoids (235 mg/g) and other phenolics (91 mg/g). *In vitro* it inhibited xanthin oxidase (IC_{50} = 7.5 μg/ml), LPS-induced NO- and PGE_2-production and iNOS- and COX-2-expression at 10, 30 and 50 μg/ml (Wu et al., 2006).

3.36. Thymelaeaceae

Daphne mezereum L. expelled slime and relieved sore joints (Fu.; Tab.).

Various species of *Daphne* have been used traditionally for inflammatory complaints: in TCM *Daphne tangutica* Maxim. is used for RA and *Daphne mezereum* is used for chronic rheumatism and gout (Chen et al., 2004). In Serbia the bark *Daphne mezereum* and *Daphne laureola* L. are traditionally boiled in vinegar and used externally for rheumatism (Jarić et al., 2007).

The ethyl acetate extract of *Daphne pontica* L. inhibited carrageenan-induced paw oedema, TPA-induced ear oedema (50 mg/kg = 22.7–32.0%; indomethacin: 10 mg/kg = 32.6–36.4% inhibition) and PGE_2-induced paw oedema significantly (50 mg/kg = 3.2–27.3%; indomethacin (10 mg/kg) = 6.3–38.3% inhibition) (Kupeli et al., 2006, 2007).

Yesilada et al. (2001) showed that the diterpenoids genkwadaphin and 1,2-dehydrodaphnetoxin and the coumarin daphnetin from *Daphne oleoides* Schreb., inhibit the proinflammatory cytokines, IL-1β, IL-1α and TNF_α at test concentrations 1–30 μg/ml The toxin daphnetoxin is found in the bark of *Daphne mezereum*. The seeds contain mezerein. These diterpene benzoic acid ortho-ethers act necrotic on the skin and damage kidney and the CNS. Consumption of just 10–12 berries may be lethal to children (Teuscher and Lindequist, 1994).

3.37. Urticaceae

Nettles (*Urtica dioica* L.) were used externally for gout of the feet and other forms of painful joints (Bo.; Fu.; Matt.; Lon.; Tab.).

The traditional use of nettles for rheumatic disorders can be followed back to Roman times (Foster and Duke, 1990). Nowadays nettles are sometimes used for symptomatic treatment of RA and OA (Chrubasik et al., 2007).

Various nettle extracts and some sub-fractions thereof have shown some activities *in vitro* and *ex vivo*: The standardised ethanolic nettle extract IDS23 inhibits COX-dependant biosynthesis of PGs *in vitro* (IC_{50} = 92 μg/ml) and LPS induced release of TNF_α and IL-1β (Obertreis et al., 1996) and inhibited NF-κB *in vitro* by stabilising the inhibitor IκB-α (Riehemann et al., 1999). There are also some results from patient questioning. Seventeen of 18 patients who used stinging nettles as an additional therapy for rheumatic pains reported that regular use of nettles subjectively helped relieve the pains without negative side effects so the doses of synthetic analgetics could thus be reduced (Randall et al., 1999).

3.38. Verbenaceae

The common vervain (*Verbena officinalis* L.) was boiled in wine and drunk to soothe pains and gout of the feet or crushed to be rubbed on the affected body parts (Bo.; Fu.; Tab.).

In European folk medicine *Verbena officinalis* has been used for over 200 years for inflammatory diseases including rheumatism (Wichtl and Bisset, 1994; Speroni et al., 2007). It is listed in the Chinese Pharmacopoeia and in the British Herbal Pharmacopoeia (Calvo, 2006).

In an ethnobotanical field study from Serbia, Jarić et al. (2007) reported that *Verbena officinalis* is known to be analgetic and antiphlogistic. In Central Italy it is used for rheumatic ailments by placing the aerial parts of the plants on the affected joints (Guarrera et al., 2005).

The main constituents in *Verbena officinalis* are iridoids (Rimpler and Schaefer, 1979; Makboul, 1986), verbascoside (Hänsel and Kallmann, 1986), flavonoids (Calvo et al., 1997), triterpene acids and sterols (Deepak and Handa, 2000).

Various different extracts of *Verbena officinalis* (petrol ether-, chloroform-, methanol extract, flavonoids enriched extract and a CO_2 extract) inhibited carrageenan-induced rat paw oedema. The strongest inhibition was achieved with the CO_2-Extrakt (Speroni et al., 2007). Antiphlogistic activities of β-sitosterol (Gupta et al., 1980), phenylpropanoids like verbascoside, iridoids such as verbenaline and hastatoside, ursolic acid and other triterpenoids have been demonstrated (Recio et al., 1995; Safayhi and Sailer, 1997).

4. Discussion and conclusions

Bock, Fuchs, Matthiolus, Lonicerus and Tabernaemontanus were physicians and naturalists who precisely observed and described nature, collected and compiled ancient knowledge from authors such as Hippocrates, Dioscurides, Galen, Plinius etc as well as from their contemporary folk medicine. They were in contact with each other and influenced one another as well as many generations of physicians and naturalists to come.

In this survey of these historic works we looked for plants that had specific application for the treatment of rheumatic disorders, and found 63 plants listed that had clear indications. Twenty-five

of them are used solely internally. Thirty-four have both an internal and an external application and three are used only externally. Amongst the families of plants Lamiaceae were most strongly represented with 8 species, Asteraceae with 7 and Apiaceae with 5. Boraginaceae, Cucurbitaceae, Pinaceae and Salicaceae were represented with 2 or 3 species, and all other families only had one species mentioned.

A number of the plants are widely used spices which originated in the Mediterranean area but were cultivated and therefore well known to the authors: *Foeniculum vulgare*, *Rosmarinus officinalis*, *Lavendula stoechas*, *Thymus vulgaris*, *Salvia officinalis*, *Salvia aethiopis* and *Helichrysum stoechas*. Others which were not originally native to Central Europe were cultivated for agricultural or ornamental reasons. These include *Physalis alkekengi*, *Rubia tinctorum*, *Avena sativum*, *Hordeum vulgare*, *Asparagus officinalis*, *Artemisia abrotanum*, *Inula helenium*, *Asphodelus albus*, *Rheum rhabarbarum* and *Smilax* sp.

Most of the plants, however, have a wider distribution and so can be found growing wild on both sides of the Alps: *Pimpinella saxifrage*, *Seseli libanotis*, *Asarum europaeum*, *Verbena officinalis*, *Saxifraga oppositifolia*, *Helleborus niger*, *Populus alba*, *Lemna minor*, *Teucrium chaemaedrys*, *Papaver rhoeas*, *Salix* sp., *Daphne mezereum*, *Urtica dioica*, *Verbena officinalis*, *Peucedanum osthruthium*, *Hypericum perforatum*, *Stachys officinalis*, *Aegopodium podagraria*, *Brassica oleracea*, *Bryonia dioica*, *Centaureum erythraea*, *Calamintha nepeta*, *Lithospermum officinale*, *Artemisia absinthium*, *Artemisia vulgaris*, *Matricaria recutita*, *Silybum marianum*, *Heliotropium europium*, *Plantago lanceolata*, *Viscum album*, *Juniperus communis*, *Papaver rhoeas*, *Primula veris*, *Primula elatior* and *Potentilla species*.

Only a few of the plants can be regarded as being not really Mediteranian but rather Central or Northern European in their distribution These include *Iris germanica*, *Scrophularia nodosa*, *Larix decidua*, *Abies alba*, *Symphytum officinale* and *Genista germanica*.

Four of the herbal remedies listed are of strictly Mediterranean origin: *Pistacia terebinthus*, *Citrullus colocynthis*, *Capparis spinosa* and *Urginea maritima* or from tropical regions: *Myristica fragrans*. They could not have been grown or collected in the author's home countries in Central Europe. The use of these plants, which would only have been available through trade, may have been adopted from ancient writings like Dioscurides or from other cultures. Tabernaemontanus reported that Rhasis (an Arabian physician, chemist, and alchemist Abu Bekr Muhammed Ben Zakeriyah er-Rasi) recommended *Capparis spinosa* juice. Bo., Matt. and Lon. also reported this remedy. Dioscurides had just described it as slime dispelling. Bo., Matt., Tab. listed *Urginea maritima* for rheumatic disorders whereas Dioscurides had just described its purgative effects (a German version of Diosurides Materia medica was accessed under: http://www.pharmawiki.ch/materiamedica/images/Dioskurides.pdf). The authors sometimes emphasised their beneficial claims by reporting that the ancient Greek and Roman scholars had already known of a plants usefullness: Tabernaemontanus reported that Plinius had already documented the use of cabbage juice, that Galen reported on *Hypericum perforatum*, that to ancient Greeks primules were the best 1"Arthritica", that also Fernelius advised using primules and that Ätius (Aetius of Amida, a 5th century physician) had recommended taking *Thymus vulgaris*. Tab. reported that Dioscurides wrote of boiling poppy (*Papaver rhoeas*) roots and drinking the broth, whereas Bock on the other hand reported that Dioscurides had advised first soaking the poppy seeds in water before drinking it. Lonicerus cited Ruellius (another author of a herbal) when recommending nettles (*Urtica dioica*). Matt. gave an account of use of *Bryonia dioica* in a certain geographic region "in Welsh land" (probably: Italy) and also mentioned that Dioscurides had reported this plant.

So the uses of some of the plants are directly derived from Greek traditions, but many other influences like regional European folk traditions, Arabic scholars etc. are visible.

Sometimes reports were supplied of famous people who had been convinced that the remedy was indeed effective. *Teurium chamaedrys* soaked in wine was sent by Genoese traiders to Emperor Charles the Fifth who then testified than many people were relieved from their suffering for years to come (Matt.).

Some descriptions of medicines are very specific and the many steps of their preparation are described in great detail. Examples for such are different complex types of schnaps (14 examples), wines (6), syrups (1), decoctions (1), confections – a type of candy – (5) and tablets (3). Some plants are to be eaten (9) or their juice drunk or rubbed on the skin (6) or they were boiled or preserved in wine, water, met or vinegar (39). Some essential oils (9) and ointments (3) were meant for rubbing onto affected joints. Baths (2) were recommended to sweat out harmful substances and bandages, made with plant decoctions were applied externally to affected limbs (22). Four of the drugs were enemas to cleanse the body from within. Some preparations are only very sparingly described, so it is not always really clear what part of the plant was to be prepared in what way.

According to the principles of allopathy (*Contraria contrariis*) medicines are divided into hot, cold, dry and moist humours. A plant with a hot and dry nature was to dispel excess thick slime, which was seen as a cause for rheumatic complaints. Interestingly enough, many of the described plants have specific mucolytic and expectorant properties and are used nowadays for treating the upper respiratory system: *Foeniculum vulgare*, *Thymus vulgaris*, *Abies alba*, *Plantago lanceolata*, *Primula* sp. etc. A number of the plants are laxants: *Brassica* sp., *Heliotropium europaeum*, *Citrullus colocynthis*, *Asphodelus albus*, *Rheum rhabarbarum* etc. This may have to do with the concept of having to cleanse ones self of a disease by ridding the body of harmful phlegm. Also the use of enemas may be explained this way.

A number of the plants are still used today for rheumatic disorders in modern medicine, folk medicine or alternative medicinal practices: *Salix* sp., *Urtica dioica*, *Myristica fragrans*, *Rosmarinus officinalis*, *Hordeum vulgare* and *Smilax* species. Willow bark – today a treasured antiphlogistic – is mentioned by all five of the authors. *Symphytum officinale*, on the other hand, was mentioned just once and *Arnica montana* was never even mentioned in the herbals in context of rheumatic disorders. In fact the absence of many alpine plants like *Arnica montana* or *Gentiana* species in the remedies is quite striking. This may be due to a general disregard 16th and 17th century naturalists and educated town folk had for the barren, poor and threatening mountains and their inhabitants.

Other plants like *Silybum marianum* and *Hypericum perforatum* are in use today for completely different indications. The value of documenting the development of a plants uses at different points in history has been reported by Heinrich et al. (2006), Pollio et al. (2008) and others.

The potentially lethal toxicity of some plants like *Asarum europaeum*, *Teucrium chamaedrys*, *Helleborus niger* and *Daphne mezereum* was a fact the old authors were well aware of. Besides medicinal uses the authors also warn about dangers. Pregnant and sick patients were not to use *Citrullus colocynthis*, and they mention the low therapeutic index of a tonic made from primules. They warn of the toxicity of *Helleborus niger* and recommend an antidote. In the case of *Teucrium chamaedrys* Tab. warned not to eat not to sour or salty foods when taking a wine made from it. In fact, the caution taken back then was sometimes less worrying than some test concentrations some of our reckless contemporaries come up with.

Of the 63 plants listed in the five herbals 38 had shown antiphlogistic activities *in vitro* or *in vivo* in some shape or form. Fourteen

plants inhibited lipoxygenases, seventeen cyclooxygenases. Six of them inhibited both LOX and COX. Eight plant extracts had an inhibitory effect on NF-κB, IL and/or TNF and seven effected iNOS. Clinical studies were found which were generally of poor scientific quality but nevertheless may support traditional or folk medicinal uses.

Some modern day authors are sometimes quite imaginative in their claims on specificity and molecular mechanisms of action. But, despite some concerns on bad test designs, unrealistically high test concentrations etc., we must state that many of the plants like *Pistacia terebinthus*, *Inula helenium*, *Matricaria recutita*, *Silybum marianum*, *Salvia aethiopis* and *Salvia officinalis*, *Salix* sp. and *Symphytum officinale* are indeed antiphlogistic and their use may be justified. The fact that over 60% of the plants recommended for the treatment of rheumatic disorders have actually shown activity in relevant assays and that some are still used today for such indications clearly shows that 16th and 17th century herbals can be a very rewarding source of knowledge. The remaining plants which have not been tested so far may be promising candidates too. Remedies found in these historic documents should be explored systematically. These herbals from the European Renaissance which so far have received little attention from modern biomedical research could be a promising source of knowledge for the rediscovery of useful remedies and the development of modern phytotherapeutics for the 21st century.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jep.2008.11.010.

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