Author(s): Frances Watkins, Barbara Pendry, Olivia Corcoran, Alberto Sanchez-Medina

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Anglo-Saxon Pharmacopoeia revisited – a potential treasure in drug discovery?

Frances Watkins, Barbara Pendry, Olivia Corcoran and Alberto Sanchez-Medina*

Medicines Research Group, School of Health and Bioscience, University of East London, Romford Road, London, E15 4LZ

*Corresponding author: Sanchez-Medina, A. (a.sanchezmedina@uel.ac.uk)

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Teaser

Modern translations provide a new opportunity to revisit the Anglo-Saxon medicinal texts, a valuable resource for discovering and developing novel compounds from native British flora.

Abstract

Three Anglo-Saxon manuscripts reporting medicinal formulations in England from the tenth century survive: the '*Old English Herbarium*', Bald's *Leechbooks* and '*Lacnunga*' which may contain new leads and insights into new medicinal uses. Previous pharmacological studies of 16th and 17th century medicinal plants reported in the Anglo-Saxon medical texts, suggest some were effective and led to the identification and isolation of new natural compounds such as matricin from *Achillea millefolium* L., a prodrug that yields chamazulene carboxylic acid, a natural profen. New insights through multidisciplinary projects could further explore the manuscript content for the discovery of metabolites with potential pharmacological applications.

Introduction

In cancer drug development over 47% of small molecules used today originate from flowering plants or are synthetic derivatives [1]. Chinese and Indian cultures consider ancient texts of medicinal plants to be valuable resources in the search for novel compounds with potential pharmacological applications. Whereas in England, the Anglo-Saxon medical manuscripts have been much maligned until recent years, where new translations of the ancient texts have provided greater access to the Anglo-Saxon pharmacopoeia for scientific investigation of this indigenous herbal tradition [2]. There have been studies of British medicinal plants appearing in later herbals although these formulations are greatly influenced by European, Arabic and Mediterannean pharmacopoeias of the time [3].

The Anglo-Saxon period spanned over 500 years from AD 499-1066. King Alfred (AD 871-899) was responsible for the foundation of English law and commissioned the Anglo-Saxon Chronicle, to record major events and natural phenomenon from

the time of Christ [4]. There is supporting evidence for the 'little optimum' or Medieval Warm Period, thought to be similar to current day British weather patterns, with 38 established English vineyards listed in the Domesday survey of 1086 [5].

For more than half a millennium battles, disease, droughts and famines in Anglo-Saxon England created great demands upon human health and the physicians attending the wounded and the sick. Leech or '*laece'* is an Old English word for healer or doctor. The Anglo-Saxon leech would have had many written sources at his disposal including Latin and Greek medical books [6,7,8] and a prior knowledge of plants and herbal practices would have been required to make effective use of the herbal texts, to confidently treat disease and charge a *laecefoh* or 'doctor's fee' for services and medication [8].

Some of the Anglo-Saxon settlements were near swamps and marshes resulting in people suffering from asthma, eye and ear infections, pleurisy and rheumatism. Spring fever, now thought to have been malaria, was recorded in the eighth century by the venerable Bede, historian and theologian, and remained evident throughout the Anglo-Saxon period. Disease encompassed plague and leprosy; battle wounds, amputations and burns; rheumatism, viral infections or '*flying venoms'* and a variety of parasites, especially '*burrowing worms'* [7, 9] . The most common remedies found in the Anglo-Saxon medical texts are for skin disease, cough or lung disease, eye problems, headaches and fevers [10].

Treatment was empirical, pragmatic and according to Cameron [7] two thirds of the remedies would have been effective for the prescribed condition. Internal and external applications were made from the whole plant or specified parts prepared as infusions, decoctions in wine or ale and pounded in animal grease for ointments,

salves and poultices. Formulas comprised ‘simples’ or single plant remedies as well as combination formulas [11] (vol 1, p11). Constant eye, skin and urinary problems suggest that people were more likely to be deficient in vitamin A during the winter months and also vitamin C, resulting in bleeding gums, scurvy, ulcers and dysentery. Exotic fruit and spices were highly valued and by the end of the tenth century, London was a vibrant trade centre exchanging goods from Europe, Africa and the East [5,12].

Anglo-Saxon Medical Manuscripts

Today, over one thousand pages of medical texts compiled in the vernacular survive of which three major works, the *Old English herbarium* (AD 950), Bald’s *Leechbooks* (AD 950-1000) and ‘*Lacnunga*’ (AD 1000) describe common conditions affecting human and animal health and their treatments during the ninth and tenth century [10].

The *Old English Herbarium* (British Library, Cotton Vitellius C.III) is believed to be a compilation of earlier European Latin texts that was in circulation in England during the 8th century, translated and reordered in Old English with Anglo-Saxon names allocated to many of the plants. At least four copies are known to have existed at the same time in Anglo-Saxon England illustrating that it was considered an important medical text possibly in general circulation to physicians [13]. Some plants illustrated are of Mediterranean origin and would not have grown in England although of the 185 plants included, 140 were given an Old English name alongside the Latin or Greek reference [7,8].

It is believed Bald’s *Leechbooks* (British Library, MS Royal, 12.D.XVII) were commissioned by Bald around AD 950 [6,8] to assimilate the best of medical

knowledge from classical sources into Old English; a unique practice not witnessed anywhere in mainland Europe during this period [2,14]. Books I and II begin with a number of remedies for each condition starting at the head and moving down the body towards the toes; the first book is complete and concerned with mainly external complaints. The second, a book of the 'inwards', shows some anatomical understanding of liver function and external symptoms of internal complaints whilst the third is thought to be of an earlier period as there is less Mediterranean influence in the formulations [15] (Bk II p.221). Generally, recipes include a list of plant names with brief directions, 'Oxa taught us this leechdom' implying that the person compiling the formulation would have had prior knowledge of how to prepare the mixture [15] (p.121).

A lesser known, and anonymous, semi-complete collection of 193 pages commonly referred to as '*Lacnunga*' (British Library, MS Harley 585) is believed to have been compiled around AD1000 and lists more than 240 Old English plant names. It is a collection of formulations from many different sources and may have been a 'commonplace' book or a lay person's collection as it contains many errors and inconsistencies [8]. *Lacnunga* does include remedies from all three *Leechbooks* although Pettit (2001) considers the collection to be derived from another exemplar now lost. Some 300 plants are reported across the three manuscripts with many still used in Western herbal medicine including *A. millefolium, Marrubium vulgare* L. and *Hypericum perforatum* L. [16].

Recent Translations Illuminate Anglo-Saxon Medical Practice

During the nineteenth century the philologist Thomas Oswald Cockayne of King's College London, achieved a monumental task in translating all known medical Anglo-Saxon manuscripts into modern English [13]. For nearly a century there was a denial

that the Anglo-Saxon texts had anything of value to offer the medical profession and were, according to Wilfrid Bonser, an archivist and historian, ‘sterile formulas, which could be applied without any exercise of reasoning, alone survived for use during the Dark Ages’ [7]. During the 1960’s attitudes began to change with scholars compiling new translations, thus opening the door for scientific investigation of the potential value of plants used in these historical texts [7,8,10,11,13].

Scholars have hotly debated the correct identity of plants cited in the texts particularly as, in some cases, the accompanying illustrations differ to the plants described; refer to a subsequent remedy or could be simply, an incorrect translation of the original text and presents one of the main barriers to the recovery of the plant identification [7,10,17]. Confusion also arises where the Anglo-Saxons used the same name for different plants. Brown plant or ‘*brunwyrt*’ may refer to some visual aspect of the plant being brown or, a disease of the mouth and throat and often, the converse was true, one plant having many different common names. The formulations give different medicinal uses for different parts of the plant including the leaves, flowers, roots, seeds, juice [7,8] and in some instances, the whole plant is specified as in a wound salve ‘…the nether and upward part of agrimony, boil in ale, barm them with yeast’ [15] (p.97).

Economic botany was a consideration for the lay physician who would have relied upon locally grown plants for the mainstay of his pharmacopeia and substituted species according to the local terrain e.g. *Plantago major* L. grows well in clay but in sandy soil *P. media* would be chosen. There was an awareness that the potency of plants varies during the growth cycle and the texts, where considered important, give specific instructions for harvesting [7,13]; a study of *H. perforatum* showed aerial

parts did not display any antimicrobial activity when harvested in July compared to activity present when collected in August [17].

Bioactive Metabolites from Anglo-Saxon Medicinal Plants

Evidence suggests some plants used in Anglo-Saxon remedies indeed have pharmacological actions relevant for treating the conditions cited in the ancient medical texts [7]. One *Leechbook* remedy for spleen pain, states 'pound green willow bark, boil it alone in honey, give it to him to eat, three pieces, having fasted overnight'[8] (p.387). Aspirin, a synthetic derivative from *Salix alba* L. or willow bark was patented in 1900 and sold as a tablet to relieve headache, muscular and joint pain. *Papaver somniferum* L. or white poppy in the *Old English herbarium* was recommended for eye pain, headache and sleeplessness 'take the juice of the plant, rub it on the person and you will quickly give him sleep' [13] (p.173). The greatest contribution to medicine has been the alkaloid group with codeine, morphine and thebaine all isolated from the white poppy [18]. A large number of plants were used in treating wounds including *Hedera helix* L. or ivy leaf and although it is no longer used in Western herbal medicine it is an important herb in European herbal medicine, particularly Germany, for treating respiratory conditions. A postmarketing study of 9657 patients taking ivy leaf syrup extract for bronchitis showed 95% improvement after 7 days administering herbal preparation [19]. Three native British plants from the ancient medical texts that have been well researched for their phytochemical potential are *A. millefolium*, *M. vulgare* and *H. perforatum.* Taken together, these *in vitro* and *in vivo* studies reveal bioactive constituents, often the major constituents, underlying the Anglo-Saxon medicinal uses.

***A. millefolium*, (Asteraceae), Yarrow**

Yarrow is an aromatic perennial plant native to the British Isles and found in grassland habitats from sea-level to 1210m. The common name is derived from the Anglo-Saxon word '*gearwe'*, modern synonyms including bloodwort, nosebleed and herba militaris which all refer to its traditional use as a wound herb [20]. It was an Anglo Saxon plant of choice for healing wounds, swellings and rashes on the face, headaches, intestinal and abdominal pain, heartburn, difficult digestion, diarrhoea, snake and dog bites. The roots were also eaten on an empty stomach for toothache [13] (p.187). Modern applications include treating digestive problems, liver and gall bladder conditions, cramps, dysmenorrhoea and fever. In Germany yarrow flower is licensed as a standard medicinal tea and in the USA it is used as a diaphoretic or febrifuge component of traditional cold and flu/fever compounds marketed as dietary supplements [20]. Recent pharmacological studies of plant extracts from all parts of *A. millefolium* have demonstrated anti-inflammatory properties [21,22], antileishmanial activity of oil from leaves and flowers [23] and *in vivo* antinociceptive effects [24]. Known *A. millefolium* constituents include matricin and other proazulenic sesquiterpene lactones known to yield chamazulene carboxylic acid (Fig. 1.), an anti-inflammatory natural profen which can inhibit COX-2 and has been used for the semi-synthesis of analogues as potential anti-inflammatory drugs [25,26]. The flavonoid constituent casticin (vitexicarpin) shows a moderate inhibition in the reduction of a water soluble tetrazolium salt and a strong inhibition of lipooxygenase with an IC_{50} value of 26 μM [27]. In terms of modern drug discovery and the search for chemical diversity from sustainable natural product sources, there exist opportunities to mine *A. millefolium* for more minor constituents and current diseases not indicated by the Anglo-Saxon manuscripts. One recent example on the antitumoral effect of casticin showed two MCF-7-derived breast cancer cell lines

MN1 and MDD2, inducing a significant G2/M cell cycle arrest and induction of apoptosis via a multiple mechanism independent of p53 mutation [28].

***M. vulgare*, (Lamiaceae), White horehound**

Marrubium or white horehound, a native to the British Isles, is found on short grassland, open or rough ground. The plant is listed in all three manuscripts for treating coughs, cold, snake bite or poisonings; a common occurrence with people collecting wild foods from the hedgerows. One remedy for cough says 'boil marrubium in water, a good deal of it, sweeten a little, give the man to drink a cup full' [15] (p315). The plant is a bitter tonic, expectorant, hypotensive, purgative, emetic and a vermifuge. Today it is traditionally used in Western herbal medicine as a daily dose equivalent to 4.5g herb, primarily for treating bronchitis and asthma [20]. Biological activity studies have shown that the alcoholic root extract of *M. vulgare* is a potent inhibitor of biofilm formation and adherence of MRSA with IC_{50} values of 32µg/mL and 8µg/mL respectively [29], which can explain the Anglo-Saxon uses for treating battle wounds [11,13]. Other *in vitro* studies have also demonstrated the hypoglycaemic, analgesic and antispasmodic effects of extracts from this plant [30]. The main chemical component in *M. vulgare*, is marrubiin, a labdane diterpene isolated from acetone and ethanol extracts of this plant [31]. Marrubiin, marrubiinic acid and marrubenol (Fig. 1) have shown potent analgesic effects *in vivo* in the writhing test (10mg/kg, i.p.) by reducing abdominal constrictions by 92, 80 and 94% respectively [30,32]. The observed analgesic effects can also be associated to the Anglo-Saxon use of this plant in treating stomach ache, painful and swollen joints and all stiffness in the body [13]. Marrubenol has also been shown to have a vasorelaxant activity induced by the blocking of L-type voltage-dependant calcium (Ca^{2+}) channels present in smooth muscle [33]. It has been demonstrated that vasorelaxation is essential for angiogenesis, an important process in wound healing

[34]. Another constituent in *M.vulgare* is ladanein (Fig.1), a methylated flavone which has shown *in vitro* cytotoxic activity against dasatinib-resistant leukaemia cells but inactive against human peripheral blood mononuclear cells or human monocytic leukaemia cells [35]. Additionally, because of its growth inhibition activity against chloroquine-sensitive *P.falciparum* (IC_{50}=9μM), ladanein was recently used as a template to design a pharmacophore to target the biosynthesis of fatty acids of this protozoan organism [36]. Another Anglo-Saxon use was to wash scabs, impetigo and ringworm with a decoction of the aerial parts [13] (p.170). Verbascoside, a phenylpropanoid glycoside (Fig.1), has shown to be active against both Gram positive and Gram negative bacterial strains and also isolated as one of the antibacterial metabolites in *Marrubium globosum* and the active antibacterial metabolite of *Buddleja globosa* [37,38].

***H. perforatum*, (Hypericaceae), St. John's Wort**

St. John's Wort or hypericum is a rhizomatous perennial native to the British Isles and found in dryish grassland, banks and open woodland. The *Old English herbarium* formulation for *H. perforatum* is to 'pound the plant and drink to stimulate urination', yet 'pound in wine and give to drink for a quartan fever '[13]. The plant also had a reputation for purifying and strengthening other plant formulations [8]. *H. perforatum* has been traditionally used as an aromatic, expectorant, anxiolytic, sedative and anti-inflammatory to treat bladder complaints, chronic catarrh, colds, diarrhoea, jaundice, rheumatism, menopause, worms and nervous depression [16,39]. *H. perforatum* has been widely tested *in vivo* and *in vitro* for a variety of pharmacological effects such as antibacterial, anti-inflammatory [40], wound-healing [41,42], antitumoral [43], antiviral [44], inhibition of dopamine and norepinephrine reuptake [45], reduction of neuropathic pain [46] and treatment of mild-to-moderate depression [47,48] among others. Hydroalcoholic extracts of *H. perforatum* contain

naphtodianthrones, flavonoids, phenylpropanes, phloroglucinols, proanthocyanidins secondary, tannins [40] but it is known that the activities mentioned before are mainly mediated by a single or a combination of hypericin, pseudohypericin and/or hyperforin (Fig. 1). Hypericin is considered a potential new tool for the photodynamic therapy of cancer [44]. Hyperforin is known to be the key contributing metabolite for antidepressant activity and the main metabolite responsible for the antibacterial activity [40,47]. Other plants now known to have therapeutic properties and used in drug development (Table 1) were evident in the Anglo-Saxon formulations and with closer inspection, the texts could provide further insights into additional pharmacological compounds from native British plants.

Conclusion and future perspectives

The stylistic illustrations in the Old English herbarium have been criticised for being too simplistic, yet are reflective of dried plants in herbarium specimens and would have been useful references to persons harvesting plant material from the wild or receiving dried material from overseas [6,13]. There were different types of medical literature ranging from the gold standard *Leechbooks* of Bald*,* combining the best of classical and indigenous teachings into a coherent text suitable for attending the royal household in Anglo-Saxon England. '*Lacnunga*' on the other hand is considered to be a lay physician's 'work in progress' or personal collection from the general formulations in circulation at the time [8,11]. The monasteries compiled their own medicinal literature comprising simple manuals for monks to attend the sick [9]. Plants allocated an Anglo-Saxon name in the *Old English herbarium* would have been considered more noteworthy than those without and, if not grown in England, available through foreign trade and monastic exchanges [7,12]. In later herbals, Culpeper [49] wrote that dandelion did not warrant a written description as it was known everywhere, showing that common knowledge of formulations was often

glossed over or omitted and subsequently would be lost to future generations. Plant diversity changes with evolving agricultural methods as seen recently with *Betonica officinalis* L. or betony [50]. This plant was popular with Anglo-Saxons and must have been readily available with over 29 single formulations in the *Old English herbarium* [13,15]. Betony favours impoverished hay meadows and in the last twenty five years has significantly declined in southern England [50]. With hindsight and the scientific evidence base still evolving, many of the ancient herbal formulations seem rational. In some cases, formulations were improved upon by adding plants to improve the efficacy. In Leechbook III a remedy previously seen in the *Old English herbarium* had been altered to include wild garlic mustard to enhance the diuretic properties of the formulation [2]. Some plants continue to be used in Western herbal medicine whilst others are no longer prescribed. Perhaps because of changing trends as new plants arrived from overseas; scarcity from over harvesting or a changing landscape; more effective plants found as a result of observations and knowledge exchanged through circulation of the medical manuscripts. Whatever the reason, certain plants fell by the wayside that could be pharmacologically active. There is evidence to suggest that the Anglo-Saxon texts as a source for developing modern pharmaceuticals: *Verbena officinalis L.* or 'berbene' was prescribed for all kinds of poison with the plant powdered and given in a drink [13] (p.179) and one of the major constituents, verbascoside, exhibits a wide range of biological activity including antimicrobial, anti-inflammatory and wound healing properties [51].

Plant use for medicinal purpose is universal across all ancient cultures with many plants identified as having similar uses in the different pharmacopoeias. Others such as *Isatis tinctoria* L. *or 'wad'* leaves are listed in the *Old English herbarium* specifically for treating snakebite and whilst no longer used in Western herbal medicine, continues to be used in traditional Chinese medicine (TCM). The Anglo-

Saxon era is often referred to as the Dark Ages and is widely perceived to have been a period of turbulence and lack of cultural development. The Anglo-Saxon pharmacopoeia reviewed here demonstrate an established system for administering plant-based treatments to the sick.

The focus here has been small molecule chemistry although the use of plant biotechnology for crafting enzyme pathways in semi-synthesis is equally an area for further exploration such as the cell suspension culture of yarrow leaves to produce melatonin [52]. In drug discovery the incremental development of high throughput *in vitro* biology and toxicology screens continues apace. However, the quest for molecular diversity remains limited by inaccessible chemistry routes and limited diversity of chemical scaffolds. Newer analytical tools for mining complex mixtures include hyphenated LC-NMR-MS spectroscopy [53] which enables greater access to active compounds that are minor constituents. Metabolomic mapping of pharmacological activity onto chemical features using multivariate data analysis is clearly a further relevant development [54]. However, the final frontier is arguably understanding the drug metabolism and pharmacokinetics aspects of novel classes of secondary metabolites, which can only fully be accessed though *in vivo* studies. Due to the perceived economic barriers to discovering drugs from plant natural products, there now exists an opportunity for truly multi-disciplinary research: social networks of linguists, botanists, herbalists, the medical profession and chemists to collaborate and recover those plants yet to be identified, as well as, investigate the pharmacological and medicinal uses of the known plants in the Anglo-Saxon pharmacopoeias [3,9].

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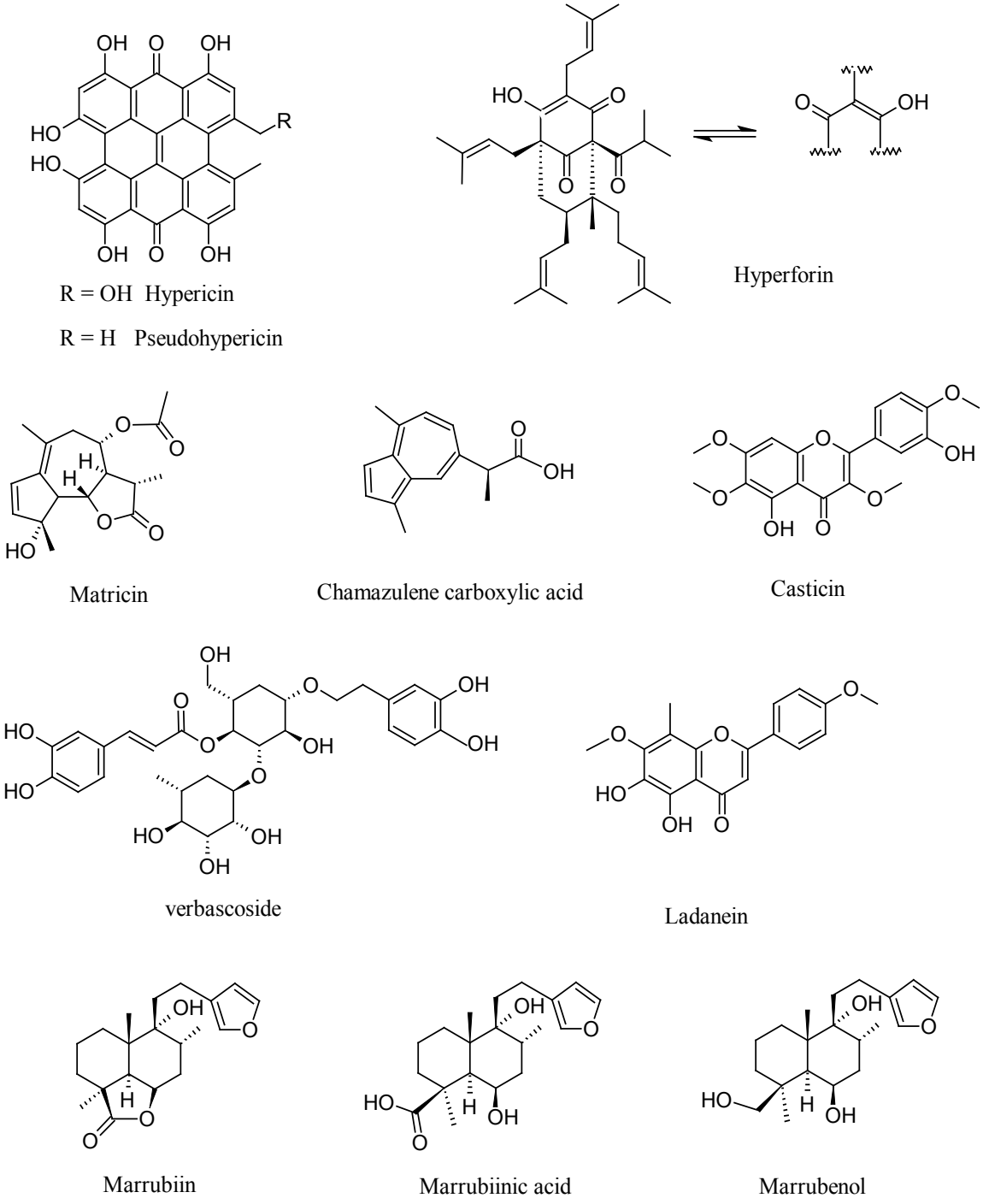

Fig. 1 Chemical compounds from *Hypericum perforatum, Achillea millefolium* and *Marrubium vulgare*.

Table1.0 Evidence of Other Plants in Anglo-Saxon Formulations

Latin, Common and Anglo-Saxon Plant Names	Relevant Anglo-Saxon Indications*	Current Western Herbal Uses**	Some Significant Constituents	Reference
Acorus calamus L. (Sweet Flag) *Beowyrt*	Root decoction for urinary retention '..within three days, the person will be able to pass urine..' (p.150)	Rhizome is used for stomach complaints such as gastritis, gastric ulcer, intestinal colic and dyspepsia. Also an appetite stimulant in anorexia nervosa. [a]	beta-asarone	Kumar *et al*., [55] Shah and Giliani,[56]
Chelidonium majus L. (Greater Celandine) *Cyleenie*	Roots mashed in wine, honey and pepper 'for dimness, pain and film in the eyes… apply to inner corners of the eyes' (p.181)	Ariel parts to treat jaundice, gallstones and gallbladder pain. Topically, the latex is applied to warts, tinea, eczema and verrucae. Subject to legal restrictions in the U.K. [b]	Coptisine, chelerythrine, sanguinarine, chelidonine	Kaminsky *et al*., [57] Hiller *et al*., [58]
Colchicum autumnale L. (Autumn crocus) *Greate wyrt*	Salve from whole plant pounded in grease and oil applied to joints and a root infused oil for pimples on the nose (p.160)	The dried corm is used to reduce joint inflammation and intense pain in acute gout. Subject to legal restrictions in the U.K. [b]	Colchicine,colchinol	Yang, [59] Edwards *et a*l., [60]
Hyoscymus nigra L. (Henbane) *Hennebelle* or *Belone*	Whole plant, juice, decoction in wine and salve for a variety of painful swellings of joints, toothache, genitals, breasts, sore feet and lung disease (p.148)	Dried leaves and inflorescences used as a sedative and smooth muscle relaxant in cystitis, renal colic and for abdominal cramping. It is also used for spasmolytic actions in asthma and pertussis. Subject to legal restrictions in the U.K. [b]	hyoscimine, scopolamine, atropine, cleomiscosin A (from seeds)	Haas, [61] Begum *et al*., [62]
Isatis tinctoria L. (Woad) *Wad*	Mashed leaves applied directly to snakebite (p.180)	Leaf extracts are used in Traditional Chinese Medicine to remove infections with excess heat, specifically encephalitis, upper respiratory infection and gastroenteritis. Root extracts, Ban Lang Gen have been used to treat patients with solid tumours and leukaemia. [c]	tryptanthrin, glucobrassicin, indirubin	Battstrom *et al.,* [63] Mohn *et al*., [64]
Plantago major L. (Greater Plantain) *Waegbraede*	Whole plant, roots, juice and seed as decoctions, salve and poultices for wounds including snakebite, intestinal worms, painful	The leaves have both diuretic and anti-haemorrhagic actions. Topically it is applied as an ointment or lotion to treat bleeding	caffeic acid derivatives, flavonoids and iridod glycosides aucubin	Samuelsen, [65] Cameron, [7]

	headaches, swollen abdomen and hot inflammations and infected wounds, hard lumps, fever, gout, (p.142)	haemorrhoids, ulcers and chronic discharging skin eruptions such as scalds, burns and wounds that refuse to heal. Internally it is used for conditions such as cystitis with haematuria, gastric ulcer, diarrhoea, irritable bowel syndrome and respiratory catarrh. [b]		
Sambucus ebulus L. (Dwarf elder) *Wealwyrt* or *Ellenwyrt*	Whole plant pounded in wine for bladder stones and snakebite and pounded roots in wine for dropsy (p. 190)*	Although the anti-inflammatory and anti-rheumatoid effects of the berry and rhizome extracts are well documented there is no current evidence of its medicinal use in Western countries. In traditional Iranian medicine it is used to treat inflammatory diseases including rheumatoid arthritis, infections and fever. [d]	Quercetin-3-o-glucoside; first example of "valeriana" acylated iridoid diglycosides bearing the uncommon D-ribohexo-3-ulopyranosyl sugar moiety; ribosome inactivating proteins Lectins, Nigrin B and Ebuline 1 transferrin conjugates	Suntar *et al*., [66] Pieri, [67] Citores *et al*., [68]
*** Anglo-Saxon Formulation Source [13] ** a) British Herbal Medicine Association [69]; b) Blumenthal, [20]; c) Alternative Medicine Review [70] and d) Shokrzadeh *et al*. [71]**				

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