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Achillea millefolium L. s.l. revisited: Recent findings confirm the traditional use

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Achillea millefolium L. s.l. – Neue Untersuchungen bestätigen die traditionelle Anwendung

Zusammenfassung. Die Schafgarbe (*Achillea millefolium* L. s.l.) wird traditionell bei krampfartigen und entzündlichen Magen-Darm-Erkrankungen, als Gallenmittel und äußerlich bei Entzündungen eingesetzt. In neuesten Untersuchungen konnte gezeigt werden, dass die Flavonoide aus der Schafgarbe spasmolytisch wirken, während die Dicaffeoylchinasäuren choleretisch aktiv sind. Außerdem wurde eine *in vitro*-Hemmung der humanen neutrophilen Elastase, einer am Entzündungsgeschehen beteiligten Protease, durch Extrakte und Fraktionen aus der Schafgarbe beobachtet, was einen zusätzlichen Hinweis zur antiphlogistischen Wirkweise von *Achillea millefolium* L. s.l. darstellt. Somit bestätigen diese Ergebnisse die volksmedizinische Anwendung der Droge.

Schlüsselwörter: Schafgarbe, phenolische Inhaltsstoffe, Spasmolyse, Cholerese, Entzündungshemmung.

Summary. Yarrow (*Achillea millefolium* L. s.l.) is traditionally used in the treatment of inflammatory and spasmodic gastro-intestinal disorders, hepato-biliary complaints and inflammation. Now we could show that the flavonoids mediated the antispasmodic properties of yarrow, whereas the dicaffeoylquinic acids caused the choleretic effects. Moreover, we observed an *in vitro*-inhibition of human neutrophil elastase, a protease involved in the inflammatory process, by extracts and fractions from yarrow, which suggests additional mechanisms of antiphlogistic action. The presented results confirm the traditional use of yarrow.

Keywords: yarrow, phenolic compounds, spasmolytic activity, choleresis, antiinflammatory activity.

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Introduction

Yarrow (*Achillea millefolium* L. s.l.) is a widespread plant from the Asteraceae family confined to the Northern hemisphere. The name of the genus originates from the ancient use as a wound-healing remedy by the Trojan hero Achilles, whereas *millefolium* refers to the deeply divided leaves. *Achillea millefolium* L. s.l. represents a highly polymorphic aggregate consisting of several taxa which differ in ploidy level, morphology and chemical composition. The traditional use of yarrow comprises the treatment of inflammatory and spasmodic gastro-intestinal disorders and hepato-biliary complaints. Moreover, it is used as an appetite-enhancing drug due to its bitter taste, for wound healing and against skin inflammations. The aerial parts of the plant are generally applied as aqueous or alcoholic extracts. Besides the traditional use of self-collected plant material, *Achillea millefolium* L. s.l. is contained in various industrial tea mixtures as well as in some phytopharmaceuticals (Amersan®, Mariazeller Magentropfen®) [1, 2].

Due to the renewed interest in herbal medicinal products the investigation of pharmacologically active compounds in medicinal plants still represents a crucial issue in rational phytotherapy, and quality, efficacy and safety of herbal medicinal products are of high importance. Having this in mind leads us to the question: What are the active principles of *Achillea millefolium* L. s.l.? Although the antiphlogistic activity has been attributed to the sesquiterpenes [3], further pharmacological effects of the plant (e. g. spasmolytic, choleretic activity) have not yet been scientifically proven nor attributed to any plant constituents. Considering the fact that yarrow also contains phenolic compounds which are known to possess various pharmacological effects encouraged us to study their contribution to the biological activity of *Achillea millefolium* L. s.l.

Phenolic Plant Compounds

Besides essential oil and sesquiterpenes – both used for the standardisation of the drug by the European Pharmacopoeia and serving as chemotaxonomic markers –

Fig. 1. Achillea millefolium L. (http://www.biologie.uni-hamburg.de/b-online/thome/band4/tafel_121.html)

yarrow also contains phenolic compounds such as flavonoids and phenolic acids. The flavonoids mainly occur as mono- and diglycosides of apigenin, luteolin and quercetin. Regarding the phenolic acids, the ubiquituous plant compound chlorogenic acid is accompanied by dicaffeoylquinic acids (DCQAs), namely 1,5-, 3,4-, 3,5- and 4,5-DCQA.

A comparative survey of Central European taxa from the *Achillea millefolium* L. aggregate by means of the phenolic compounds outlined their chemotaxonomic relevance, particularly for the distinction of the diploid taxa [4]. Moreover, the examination of forty commercial samples of yarrow revealed that the amount of phenolic compounds in the plant was quite high, with an average content of 0.60% flavonoids and 1.48% phenolic acids [5].

Due to their polar structure phenolic substances are highly soluble in water and alcohol that are used for teas and tinctures, the common application forms of yarrow, and therefore their pharmacological activity is of special interest.

Pharmacological Effects

As mentioned above, the antiphlogistic activity of yarrow was shown to be mediated by the sesquiterpenes [3]. However, the spasmolytically and choleretically active principles of the plant are still unknown. Hypothesising that phenolic compounds might induce the respective effects, which are of high relevance for the traditional application of *Achillea*, we fractionated a crude extract from yarrow by solid phase extraction in order to enrich the dicaffeoylquinic acids and the flavonoids in two different fractions, that could succeedingly be used for biological testing.

Spasmolytic Activity

As flavonoids are known to possess antispasmodic properties, we tested the fraction enriched in flavonoids on isolated guinea-pig ilea in comparison to pure flavonoids from yarrow and flavonoid metabolites. Indeed, we observed a dose-dependant decrease in force of contraction by the flavonoid-fraction.The flavonoid aglycons were more active, the monoglycosides less active than the fraction, whereas the diglycoside rutin and the flavonoid metabolites homovanillic and homoprotocatechuic acid exhibited no effect in the tested concentration range. Furthermore, the antispasmodic activity of the flavonoid-fraction was shown to be mainly caused by blockade of the calcium inward current and – to a smaller extent – also by mediator-antagonistic effects [6].

Choleretic Activity

Dicaffeoylquinic acids (DCQAs), substances that were reported to exert choleretic effects, are also present in yarrow which prompted us to test a fraction enriched in these compounds in the isolated perfused rat liver. Cynarin (1,3-DCQA), the choleretically active principle of artichoke (*Cynara scolymus* L.), was used as positive control. In fact, the DCQA-fraction from yarrow caused a concentration-dependant increase in bile flow. Interestingly, the choleretic effect of the fraction was two- to three-fold higher than that of cynarin [7].

Antiphlogistic Activity

The antiphlogistic activity of the sesquiterpenes has been thought to be caused by interference with the arachidonic acid metabolism [8]. However, inflammation is a highly complex process and antiphlogistic drug therapy might be mediated via multiple targets. For example, the serine protease human neutrophil elastase (HNE) and the matrix metalloproteinases MMP-2 and -9 are known to be involved in the inflammatory process, particularly during chronic inflammation. Hence, inhibition of these enzymes might additionally contribute to the antiphlogistic activity of *Achillea sp*. Indeed, we observed a dose-dependant inhibition of HNE and – to a smaller extent – of MMP-2 and -9 by extracts and fractions from yarrow *in vitro*, which gives a first hint about further antiphlogistic effects of *Achillea sp*. [5].

Conclusions

To sum up, the presented results confirm the traditional use of yarrow: while the spasmolytic activity was attributed to the flavonoids, the dicaffeoylquinic acids were shown to mediate the choleretic effects. In addition to the antiphlogistic activity caused by the sesquiterpenes fur-

ther possible targets for the antiinflammatory effects of the plant were found. Hence, these findings represent a valuable contribution to rational phytotherapy and justify the traditional use of *Achillea millefolium* L. s.l. in the treatment of spasmodic and inflammatory gastro-intestinal complaints, hepato-biliary disorders and inflammation.

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