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·Reviews·

Current natural products with antihypertensive activity

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[ABSTRACT] Natural products have been an important source of new drugs, which also played a dominant role in the discovery and research of new drugs for the treatment of hypertension. This review article reviews the recent progress in the research and development of natural lead compounds with antihypertensive activity, including alkaloids, diterpenes, coumarins, flavonoids, and peptides. We summarized their structures, sources, as well as the antihypertensive mechanisms. These information provides instructive reference for the following structural modifications and optimization.

[KEY WORDS] Natural products; Antihypertensive activity; Lead compounds; Action mechanism

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Introduction

Natural products have been an exemplary source of new drugs, and many of the currently available medicines have been directly or indirectly derived from them, which is particularly evident in the areas of cancer and infectious diseases [1-2]. Meanwhile, the influence of natural product is also quite evident in other areas [3]. The research, development, and use of natural products as therapeutic agents, especially those derived from plants, have been increasing in recent years.

Hypertension has become one of the most important preventable causes for premature morbidity and mortality worldwide. It is estimated to cause 7.5 million deaths, about 12.8% of all annual deaths [4-5]. Most of the currently used antihypertensive agents cannot be used as a single drug therapy because of their limited efficacy and side effects. Therefore, the research and development of new drugs with multiple therapeutic effects is most desirable [6].

The treatment of hypertension with plant extracts or plant-derived products is well documented. Some plant sources of antihypertensive natural products were listed in Fig. 1. However, references about isolation, identification and mechanism research of the lead compounds really contributive to antihypertensive activity are still limited. In this review article, we discuss the recent progress in the research of natural lead compounds with antihypertensive activity, emphasizing the mechanisms underlying their antihypertensive action.

Alkaloids

(+)-Dicentrine

(+)-Dicentrine (Compound **1**, Fig. 2) is an alkaloid aporphine derivative isolated from the plant *Lindera megaphylla* and *Actinodaphne sesquipedalis*. Several *in vitro* and *in vivo* evaluations have proven that this alkaloid is a good candidate for treatment of hypertension and other cardiovascular diseases. After oral administration of (+)- dicentrine (5 and 10 mg·kg^{-1}, twice a day) for 4 weeks, the mean arterial pressure (MAP) in spontaneously hypertensive rats (SHRs) decreased from 160 mmHg to 102 mmHg, and the declining rates was 36.3% [7]. However, a higher dose of (+)-dicentrine (10 mg·kg^{-1}, i.v.) did not cause any significant changes in heart rate (HR), cardiac output (CO), or stroke volume (SV) [8]. Mechanistic research has shown that (+)- dicentrine is an α_1-adrenocepter antagonist which is more selective towards the putative α_{1D}-adrenocepter subtype of the rat aorta than the α_{1B}-adrenocepter subtype of the spleen [9].

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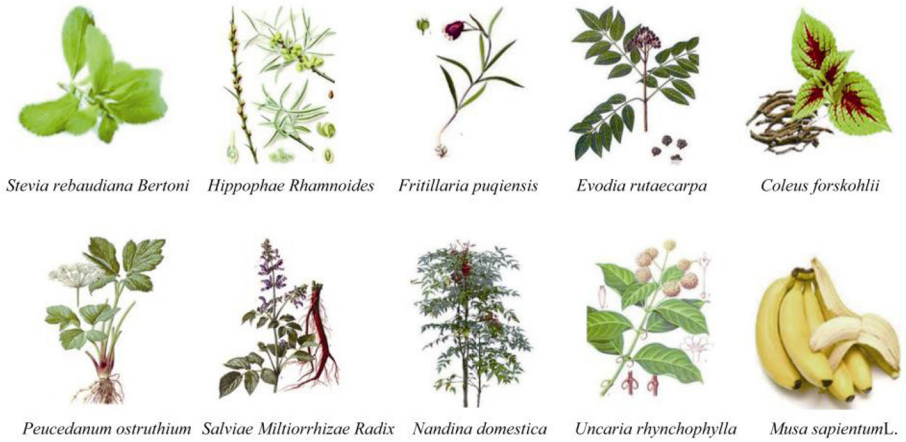

Fig. 1 Some plant sources of antihypertensive natural products

Laurotetanine

The leaves of *Luureliu sempervirens* (Monimiaceae), an endemic Chilean tree known as "Laurel", are used by the Mapuche Amerindians for treating headache and as a diuretic. Intravenous administration of a hydroalcoholic *L. sempervirens* extract to rats, elicited a hypotensive response of (−27.0 ± 2.0)% in the MAP of normotensive animals at a dose of 5 mg·kg^{-1}. In an acute oral toxicity study, "Laurel" was proven to be a very low toxicity crude drug at doses up to 3 g crude extract. Bioassay-guided isolation led to the alkaloid laurotetanine (Compound **2**, Fig. 2) as the main hypotensive principle of *L. sempervirens*leaves. Laurotetanine (1 mg·kg^{-1}) produced a hypotensive response of (−29.0 ± 2.1)% in the MAP of normotensive rats, with a duration of 2 min, which was comparable to that of the crude extract at 5 mg·kg^{-1} [10].

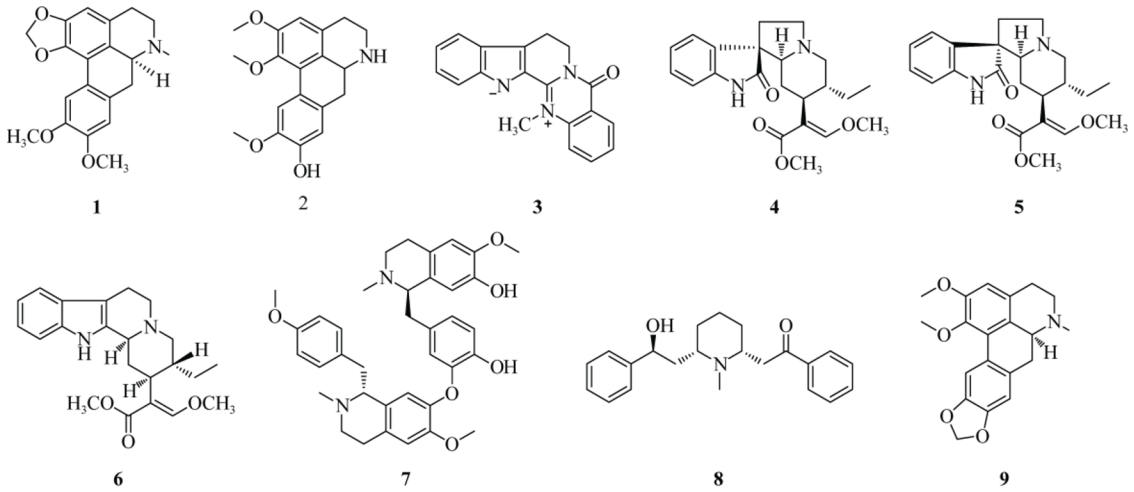

Fig. 2 Chemical structures of Compounds 1–9

Dehydroevodiamine

Dehydroevodiamine (DeHE) (Compound **3**, Fig. 2) is an isoquinazolinocarboline alkaloid isolated from the Chinese herbal drug Wu Chu Yu, the dried unripe fruit of *Evodia rutaecarpa*, which has been shown to produce vasorelaxant and hypotensive effects. Biological tests have demonstrated that DeHE induces relaxation in precontracted rat isolated mesenteric arteries in a concentration-dependent manner. The underlying mechanisms may be complex, involving interaction with the endothelium through the NO-guanylyl cyclase pathway, α-adrenoceptor blockade, K^+ channel activation, and Ca^{2+} channel blockade [11].

Rhynchophylline and isorhynchophylline

Uncaria rhynchophylla is one of the original plants of the important Chinese crude drug, "Gouteng", which is mainly used for the treatment of hypertension. Rhynchophylline (Compound **4**, Fig. 2) and isorhynchophylline (Compound **5**, Fig. 2) are the main hypotensive constituents in *Uncaria rhynchophylla*. Studies have shown that the properties of rhynchophylline and isorhynchophylline are very similar and that the latter undergoes rapid transformation into the former in acidic medium. The hypotensive potency of Compound **5** (lowering of MAP by 42.0%) is much stronger than that of Compound **4** (lowering of MAP by 32.1%) in anesthetized rats. In anesthetized thoracotomized dogs, Compound **5** (1 mg·kg^{-1}, i.v.) reduced the mean arterial pressure, heart rate, and coronary blood flow by (3.58 ± 0.19) kPa, (26 ± 18) beats/min, and (0.10 ± 0.04) mL·min^{-1}·g^{-1}, respectively. The