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Review

Characterization of diarylheptanoids: An emerging class of bioactive natural products

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ABSTRACT

Diarylheptanoids are a class of secondary plant metabolites with a wide variety of bioactivity. Research on their phytochemistry and phytoanalysis is rapidly growing and the number of identified structures bearing the aryl-C_7-aryl skeleton is at present approaching 500. Historically, the yellow pigment curcumin has been characterized as the first diarylheptanoid and the extensive research on naturally occurring analogues is still ongoing. In this review, studies dealing with the characterization of linear and cyclic derivatives are discussed from the phytoanalytical point of view. Isolation, fractionation and purification strategies from natural sources along with their chromatographic behavior and structural characteristics are discussed. The role of various techniques used for the extraction (such as Soxhlet extraction, sonication, maceration/percolation, microwave-assisted extraction, supercritical carbon dioxide extraction); isolation (liquid–liquid extraction, column chromatographic techniques, preparative thin-layer and high-performance liquid chromatography, centrifugal partition chromatography, counter-current chromatography); separation (thin-layer chromatography, high-performance liquid chromatography, gas chromatography, capillary electrophoresis) and structural characterization (UV/Vis spectroscopy, infrared spectroscopy, X-ray crystallography, mass spectrometry, nuclear magnetic resonance spectroscopy and circular dichroism spectroscopy) are critically reviewed.

Contents

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1. Introduction

Diarylheptanoids, characterized by a 1,7-diphenylheptane skeleton, constitute a group of natural products gaining emerging interest over the last few decades due to their remarkable biological activities. The more than 400 diarylheptanoids that have been identified so far [1] can be divided into linear or macrocyclic compounds. In diarylether- and biaryl-type constituents the aromatic rings are connected to form [7.1]-*meta,para*- or [7.0]-*meta,meta*-cyclophanes, respectively (Fig. 1) [1–4].

The aromatic rings of linear diarylheptanoids are often hydroxylated or methoxylated. C-4′ and C-4″ hydroxyl groups can be acetylated or glycosylated, compounds with unsubstituted aromatic rings are scarce. The aliphatic C_7 chain is either saturated or can have up to three double bonds. Further possibility is the presence of carbonyl groups at C-3 and/or C-5 (Table 1). The C-5 can be substituted by a hydroxyl group that may be free or engaged in another function: methyl, acetyl, sulfate or glycosyl groups can be attached. Diarylheptanoids can occur as mono-, di- or triglycosides. The sugar moieties may be further substituted by phenolcarboxylic acids [1,2,4,5].

According to Lv and She [1,2] (Table 1), linear diarylheptanoids can be divided into several classes. There are compounds, where a 1,5- or a 3,6-oxy bridge (a pyran or a furan ring) is formed within the C_7 chain (Fig. 2) [6]. Diarylheptanoids can also possess flavonoid (e.g. chalcone, flavanone) moieties at C-5 or C-7 (Fig. 2.) [7]. Dimeric compounds with antiproliferative activity were also isolated from *Alpinia* species, additionally, a chalcone moiety can also be attached to the dimeric diarylheptanoid skeleton [8,9]. The monomeric units can be linked through a pyridine moiety, too (Fig. 2) [10]. Diarylheptanoids bearing a special structure such as 1,3- and 1,5-diarylheptanoids comprise the last class (Table 1) [2,11]. Compounds conjugated to an ellagitannin [12] or a gallotannin unit [13] as well as those with a monoterpene [10] or a sesquiterpene moiety [14] have also been reported. Linear diarylheptanoids are abundant in plants of the genera *Curcuma*, *Zingiber*, *Alpinia* (Zingiberaceae), *Alnus* and *Betula* (Betulaceae) [1–3].

Cyclic diarylheptanoids are distributed in *Myrica* (Myricaceae), *Acer* (Aceraceae), *Garuga* (Burseraceae), *Corylus*, *Betula*, *Carpinus* (Betulaceae), and *Juglans* (Juglandaceae) species. The heptane chain of diarylether-type and biaryl-type cyclic diarylheptanoids can be saturated or unsaturated, and carbonyl or hydroxyl groups may also be attached. The aromatic rings can be hydroxylated or methoxylated at certain carbon atoms, *O*-glycosylation can also occur (Figs. 1 and 2) [1–4,15]. A special compound with an ether bond between the side chain and the aryl group has also been isolated (Figs. 1 and 2) [16].

Diarylheptanoids have been reported by numerous studies to possess diverse bioactivities including anti-inflammatory [17], pro-apoptotic [18], anti-influenza [19], anti-emetic [20], and estrogenic [21] actions, being their anti-cancer activity that basically has caught the interest of researchers. *In vitro* and *in vivo* cytotoxicity against human cancer cell lines of diarylheptanoids has been shown [22,23]. *In vivo* citotoxicity of oregonin (Fig. 2) has been proved in the B16 murine melanoma model [24]. Although a paper doubting the biological activity and therapeutic utility of curcumin (Fig. 2) – due to its unstable, reactive and non-bioavailable properties – has recently been published [25], the interest towards curcuminoids and diarylheptanoids is still undiminished.

2. Extraction and isolation of diarylheptanoids

2.1. Extraction

There are two prevalent strategies for the extraction of diarylheptanoids. The first method involves the extraction carried out under reflux, in a Soxhlet apparatus, by sonication, or by maceration/percolation with organic solvents such as chloroform, dichloromethane, ethyl acetate, methanol/ethanol, aqueous methanol/ethanol. Although a certain loss may occur, this method allows simple extraction of diarylheptanoids. The initial step is usually followed by subsequent liquid–liquid extractions with hexane, chloroform, ethyl acetate, ethanol, or *n*-butanol [26–31]. The alternative option for diarylheptanoid extraction employs sequential solvent extraction with hexane, chloroform, or ethyl acetate, followed by methanol, ethanol or *n*-butanol [32–34]. A selection of the methods applied in diarylheptanoid extraction and isolation is presented in Table 2.

Extraction techniques aiming to reduce the need for solvents, the extraction time and the costs of producing plant extracts have been developed. In supercritical (and subcritical) fluid extraction (SFE) carbon dioxide is used as the main solvent, thus the consumption of organic solvents can be minimized. With the addition of organic modifiers, higher yields of polar target compounds and a broader range of the extracted constituents can be achieved [48].

Supercritical carbon dioxide extraction [49] and subcritical water extraction [50] have been used to obtain diarylheptanoids from plant materials. Turmeric (*Curcuma longa*) rhizomes were extracted with supercritical carbon dioxide as well as with supercritical carbon dioxide and ethanol as co-solvent. The addition of ethanol increased the extraction yield of curcuminoids and decreased the solvent consumption. Curcumin is insoluble in water, poorly soluble in hydrocarbon solvents, and soluble in alcohols. Ethanol promoted the solubilization of the polar substances (e.g. diarylheptanoids) present in the rhizomes [51]. Supercritical fluid extraction (SFE) coupled to supercritical fluid chromatography (SFC) has been applied for the analysis of *C. longa* rhizomes. The absence of curcumin in the extracts obtained by pure carbon dioxide was confirmed. The addition of methanol enabled the extraction of the curcuminoids, more than 90% recovery for curcumin was

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