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In vitro chemopreventive potential of fucophlorethols from the brown alga *Fucus vesiculosus* L. by anti-oxidant activity and inhibition of selected cytochrome P450 enzymes

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ABSTRACT

Within a project focusing on the chemopreventive potential of algal phenols, two phloroglucinol derivatives, belonging to the class of fucophlorethols, and the known fucotriphlorethol A were obtained from the ethanolic extract of the brown alga *Fucus vesiculosus* L. The compounds trifucodiphlorethol A and trifucotriphlorethol A are composed of six and seven units of phloroglucinol, respectively.

The compounds were examined for their cancer chemopreventive potential, in comparison with the monomer phloroglucinol. Trifucodiphlorethol A, trifucotriphlorethol A as well as fucotriphlorethol A were identified as strong radical scavengers, with IC_{50} values for scavenging of 1,1-diphenyl-2 picrylhydrazyl radicals (DPPH) in the range of 10.0–14.4 μg/ml. All three compounds potently scavenged peroxyl radicals in the oxygen radical absorbance capacity (ORAC) assay. In addition, the compounds were shown to inhibit cytochrome P450 1A activity with IC_{50} values in the range of 17.9–33 μg/ml, and aromatase (Cyp19) activity with IC_{50} values in the range of 1.2–5.6 μg/ml.

1. Introduction

Cancer chemoprevention describes the use of nutrients and/or pharmaceutics to block, inhibit, or reverse tumor development at various steps during the initiation, promotion, or progression phase of carcinogenesis (Surh, 2003). To identify novel chemopreventive agents, we have established a series of *in vitro* test systems which cover a broad spectrum of mechanisms relevant for the prevention of cancer in humans, including radical scavenging effects and anti-oxidant mechanisms, the modulation of phase 1 and 2 drug metabolism, anti-hormonal properties, anti-inflammatory activities, and anti-proliferative mechanisms (Gerhäuser et al., 2003). Several of the reported biological activities of algal phenols, such as anti-oxidant potential (Shin et al., 2006; Chkhikvishvili and Ramazanov, 2000; Jimenez-Escrig et al., 2001; Kang et al., 2003, 2005; Kim et al., 2004; Cerantola et al., 2006), anti-inflammatory activity (Shin et al., 2006; Shibata et al., 2003), and activation of Nrf2-mediated enzyme induction (Kang et al., 2007) have been associated with cancer chemopreventive potential. To explore the therapeutic potential of phlorotannins in detail pure compounds were isolated during the current study from the extract of *Fucus vesiculosus* L.

The brown alga *F. vesiculosus* is a member of the family Fucaceae, belonging to the order Fucales. It grows in the rocky mid-littoral and intertidal temperate coasts of Europe and North America (Lüning, 1985). Brown algae of the order Fucales contain three types of phlorotannins, all merely consisting of phloroglucinol subunits. Depending on the type of connection between the subunits these phlorotannins are termed fucols, where phloroglucinol units are connected by aryl-aryl bonds, fucophlorethols with ether and aryl–aryl bonds (Fig. 2) and phlorethols with only ether bonds present. From *F. vesiculosus* 15 fucophlorethols and four fucols with three to eight and two to four units of phloroglucinol, respectively, were described (Ragan and Glombitza, 1986). During most of these studies extracts were derivatized and the compounds subsequently isolated in their acetylated form (Glombitza et al., 1975, 1977; Preuss, 1983). The isolation of the free phenols is due to their instability a challenging task and was reported from *F. vesiculosus*

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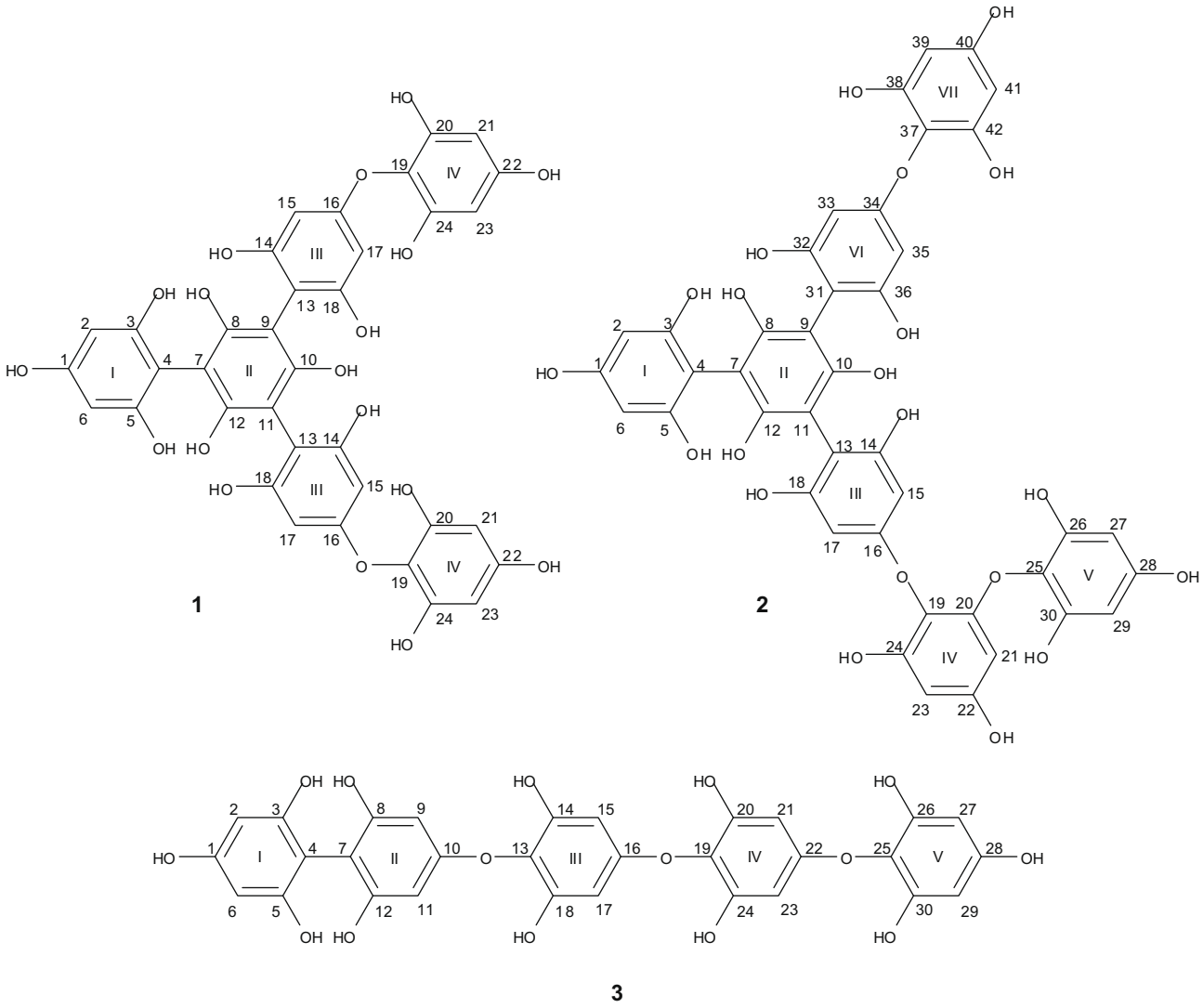

Fig. 1. Structures of compounds **1**–**3**.

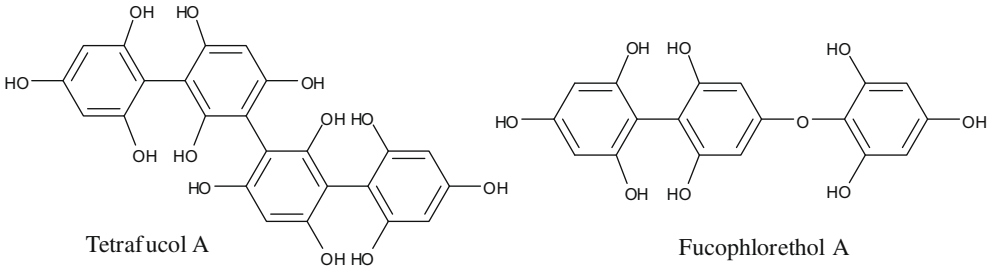

Fig. 2. Phlorotannins of *F. vesiculosus*.

only once (Craigie et al., 1977). Furthermore, cleavage products of high molecular weight phenols in *F. vesiculosus* were isolated and analyzed (Glombitza and Lentz, 1981).

Phlorotannins have been shown to be of ecological importance. They protect the producing organism against UV irradiation (Pavia et al., 1997; Swanson and Druehl, 2002), deter herbivores (Ragan and Glombitza, 1986; Pavia et al., 1997; Boettcher and Targett, 1993; Schoenwaelder, 2002) and act against pathogens (Ragan and Glombitza, 1986). Several pharmacological activities have been reported for this class of compounds including enzyme inhibition, anti-oxidative activities and antibacterial effects (Shin et al., 2006; Chkhikvishvili and Ramazanov, 2000; Jimenez-Escrig et al., 2001; Kang et al., 2003, 2005; Kim et al., 2004; Linares et al., 2004; Shibata et al., 2003; Nagayama et al., 2002). Sandsdalen et al. (2003) determined the antibacterial effects of compounds isolated from an extract of *F. vesiculosus*. One of these antibacterial compounds, i.e. fucodiphlorethol A is composed of four units of phloroglucinol and belongs to the class of fucophlorethols.