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*Full Length Research Paper*

# Biological activities of lignans from *Taxus baccata* L. growing in Turkey

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**Phytochemical investigation of *Taxus baccata* L. (Taxaceae) by successive chromatographic methods resulted in the isolation of the lignans; lariciresinol (1), taxiresinol (2), 3'-demethylisolariciresinol-9'-hydroxyisopropylether (3), isolariciresinol (4) and 3-demethylisolariciresinol (5) as well as taxoids. Compounds 1 - 5 were evaluated for their several biological activities such as anti-inflammatory, antinociceptive, anti-ulcerogenic, antimicrobial, cytotoxic, and antioxidant as well as acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and lipoxygenase (LOX) inhibitory activities. In this review, the diverse biological activity profiles of lignan derivative compounds (1 - 5) obtained from *T. baccata* growing in Turkey will be discussed.**

**Key words:** *Taxus baccata*, taxaceae, lignans, anti-inflammatory, antinociceptive, anti-ulcerogenic, antimicrobial, cytotoxicity, enzyme inhibitory, antioxidant.

## INTRODUCTION

*Taxus baccata* L. (European yew) is an evergreen and widespread shrub commonly used for ornamental landscaping. It belongs to the family Taxaceae that includes five genera. Genus *Taxus* L. is represented by eight species and two hybrids worldwide that widely distributed in the northern hemisphere, occurring in Europe, North America, Eastern Asia and Asia Minor (Van Rozendall et al., 1999).

The English yew *T. baccata* L. is a widespread plant frequently cultivated as an ornamental in gardens. *T. baccata*, a well-known poisonous plant, is the single representative in the flora of Turkey (Davis and Cullen, 1965). All plant parts with the exception of the arillus, which is enveloping the seeds, contain toxic taxine alkaloids (Wilson et al., 2001). They have been implicated in many human and animal poisonings. Although due to the toxic taxane alkaloid content it has rarely been documented as a folk remedy. In historical documents, this plant was recommended to be used as antimalarial and antirheumatic in the Roman period (Bryan-Brown, 1932; Appendino, 1993). In Ayurvedic medicine it was known indigenously as Talispatra, and is reported to be used as emmenagogue, sedative, antispasmodic and aphrodisiac (Bryan-Brown, 1932; Shanker et al., 2002), as well as against asthma (Singh, 1995). It was also listed in Avicenna's cardiac drugs, namely Zarnab (Tekol, 1989). In Turkish folk medicine, it is reported to be used as sedative and stomachic (Baytop, 1999).

The discovery and isolation of paclitaxel from the bark of the Pacific yew *Taxus brevifolia* Nutt. (Wani et al., 1971) and its introduction in cancer chemotherapy has attracted scientists to investigate the constituents of other *Taxus* species worldwide. Therefore, genus *Taxus* has been one of the most intensely studied genus in all plant genera. So far, the isolation of a large number of taxoids as well as lignans, flavonoids, steroids and sugar derivatives has been reported from different parts of various *Taxus* species (Baloglu and Kingston, 1999; Parmar et al., 1999). Our phytochemical investigation on the chloroform-soluble portion of the ethanol extract of the heartwood of *T. baccata* growing in Turkey by successive chromatographic methods resulted in the isolation of six taxoids (Erdemoglu and Sener 2000; Erdemoglu et al., 2001) and five lignans; namely lariciresinol (1), taxiresinol (2), 3'-demethylisolariciresinol-9'-hydroxyisopropylether (3), isolariciresinol (4) and

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3-demethylisolariciresinol (5) (Erdemoglu et al., 2003; 2004a).

Lignans are one of the important classes of secondary metabolites. They have been so far reported with many desired biological activities (Rios et al., 2002). In continuation of our studies on screening of Turkish medicinal plants and their secondary metabolites to be used potential leading compounds for health benefits, therefore, we have been screened the lignans obtained from *T. baccata* for several biological activities using *in vivo* bioassay or *in vitro* methods. In this review, these lignans (Figure 1) were discussed for their diverse pharmacological activity profiles such as anti-inflammatory, antinociceptive, anti-ulcerogenic, antimicrobial, cytotoxic, antioxidant and enzyme inhibitory activities.

## BIOLOGICAL ACTIVITIES OF ISOLATED LIGNAN DERIVATIVES

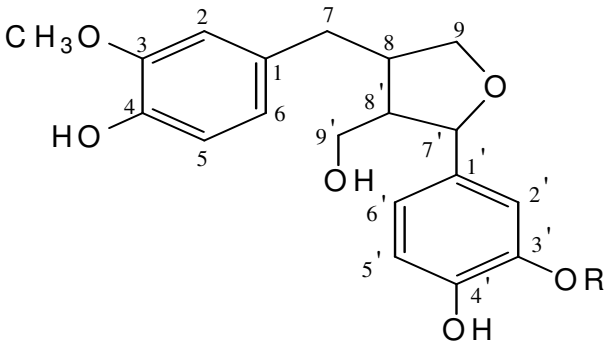
Five lignans; namely, lariciresinol (1), taxiresinol (2), 3'-demethylisolariciresinol-9'-hydroxyisopropylether (3), isolariciresinol (4), and 3-demethylisolariciresinol (5) were isolated from the heartwood of *T. baccata* and their structures were identified by using extensive spectroscopic techniques. Lariciresinol and taxiresinol were elucidated as dibenzylbutane type lignans, while 3'-demethylisolariciresinol-9'-hydroxyisopropylether, isolariciresinol, and 3-demethylisolariciresinol were determined as aryltetralin type lignans (Erdemoglu et al., 2003; 2004a). Among the lignan derivatives, although lariciresinol (1) and taxiresinol (2) were also previously reported from various other *Taxus* species (Mujumdar et al., 1972; Chattopadhyay, 1997; Kawamura et al., 2000) along with other plant species (Raju and Pillai, 1989; Okunishi et al., 2001), 3 and 5 were identified as new lignans of isolariciresinol derivatives. Moreover, 3 is the first example of a lignan attached a hydroxyisopropyl group at C-9' (Erdemoglu et al., 2003). Isolariciresinol (4) was previously isolated from other *Taxus* species (Erdtman and Tsuno, 1969; Das et al., 1993) as well as other plants (Weinges, 1961; Raju and Pillai, 1989).

Lignans, dimeric phenylpropanoids, are a large and varied group of natural products which widely distributed in the plant kingdom (Cole and Wiedhopf, 1978). Up to date, a great number of pharmacological effects have been ascribed to lignans such as antibacterial, antifungal, antiviral, antioxidant, anticancer, and anti-inflammatory (MacRae and Towers, 1984; Rios et al., 2002). In our previous studies on the lignan derivative compounds (1 - 5) obtained from *T. baccata*, we have been determined to possess their significant biological activities (Erdemoglu and Sener, 2001; Kupeli et al., 2003; Gurbuz et al., 2004; Erdemoglu et al., 2004b; Kucukboyaci et al., 2009). In addition, in these studies, molecular mechanic and semi-empirical calculations of these compounds (1 - 5) have been carried out by using MM3, PM3 and AM1 programs to obtain three dimensional-most probable geometries by using X-ray crystal structure results of similar compounds. Besides, three dimensional and the most probable structure of these compounds were obtained, compared and discussed (Erdemoglu et al., 2003; 2004a).

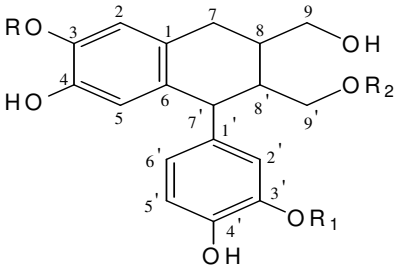
In order to evaluate the antirheumatic activity of the plant, *in vivo* anti-inflammatory and antinociceptive activity of the isolated five lignans (1 - 5) were investigated. All the compounds were shown to possess significant antinociceptive activity against *p*-benzoquinone induced abdominal stretching and significantly inhibited carrageenan-induced hind paw edema in mice. The inhibitions of isolated lignans from *T. baccata* at 100 mg/kg against *p*-benzoquinone induced abdominal stretching were ranged in the following descending order: lariciresinol (42.7%), taxiresinol (37.8%), 3'-demethylisolariciresinol-9'-hydroxyisopropylether (35.4%), 3-demethylisolariciresinol (33%) and isolariciresinol (31.3%) (Kupeli et al., 2003). These results were in accordance with the previous study of Cho et al. (2001a), where lariciresinol and isolariciresinol were reported to possess potent *in vitro* inhibitory effect on tumor necrosis factor α (TNF- α) production, a pro-inflammatory cytokine (Cho et al., 2001b).

Due to the gastric damage induced by current NSAIDs, agents with potent anti-inflammatory and antinociceptive activity without inducing gastric lesions would highly be appreciated (James and Hawkey, 2003). On the other hand, *Taxus* species were also documented to be effective in gastric complaints and used as stomachic in traditional medicine (Baytop, 1999). Therefore, *in vivo* anti-ulcerogenic potency of these compounds was investigated on ethanol-induced ulcerogenesis model in rats at two different doses, 50 and 100 mg/kg. All compounds were showed to possess significant anti-ulcerogenic activity at both doses. The effect of taxiresinol (2) was the most prominent (ulcer inhibition: 82.2% by 50 mg/kg and 85.3% by a 100 mg/kg dose). Isolariciresinol (4) and lariciresinol (1) exerted marked and dose-dependent protection against gastric lesions induced by ethanol (ulcer inhibition: 58.2-80.3% and 48.3 - 76.6%, respectively) at doses of 50 and 100 mg/kg (Gurbuz et al., 2004).

The ethanol extract of the heartwood of *T. baccata* has also been tested for antimicrobial activity. The antibacterial and antifungal activities of the extract were tested against standard strains of the bacteria (Gram-positive bacteria; *Staphylococcus aureus* and *Streptococcus pyogenes*, and Gram-negative bacteria; *Escherichia coli*, *Pseudomonas pseudomalli*, *Salmonella typhi*, *Shigella boydii*, *Enterobacter cloacca*, and *Vibrio cholera*) and the fungi (*Nigrospora oryzae*, *Microsporum canis*, *Epidermophyton floceasum*, *Drechslera rostrata*, *Aspergillus niger*, *Candida albicans*, *Curvularia lunata*, *Stachbotrys atra*, and *Pleuralus astreatus*). The ethanol



| | R |
|---|---|
| **1.** (-)-Lariciresinol | $CH_3$ |
| **2.** (-)-Taxiresinol | H |



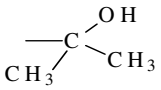
| | R | $R_1$ | $R_2$ |
|---|---|---|---|
| **3.** (-)-3'-Demethylisolariciresinol-9'-hydroxyisopropylether | $CH_3$ | H |  |
| **4.** (-)-Isolariciresinol | $CH_3$ | $CH_3$ | H |
| **5.** (-)-3-Demethylisolariciresinol | H | $CH_3$ | H |

**Figure 1.** Structural formulas of investigated compounds (1 - 5).

extract of *T. baccata* exhibited significant activity at 2 mg/ml concentration against some Gram-negative bacteria, *P. pseudomalli*, *S. typhi*, and *E. cloacca*, as compared to ampicillin and tobramycin, by determining their inhibition zones as 7, 5.5 and 8.5 mm respectively, whereas it was completely inactive against tested Gram-positive bacteria. However, it showed interesting antifungal activity at 400 µg/ml as comparable to that of griseofulvin (10 µg/ml) against *N. oryzae*, *M. canis*, *E. floceasum*, *C. lunata*, and *P. astreatus* (Erdemoglu and Sener, 2001). In a follow-up study, a chloroform-soluble portion of the ethanol extract from the heartwood of *T. baccata* and three lignan derivatives (2, 3, 5) were also tested for antimicrobial activities. According to the antibacterial activity results, only the chloroform-soluble portion of the ethanol extract from the heartwood of *T. baccata* exhibited moderate antibacterial activity against Gram-negative bacterium *P. aeruginosa* at 1 mg/ml concentration compared to imipenem at 10 µg/ml by measuring the diameter of the inhibition zones as 11 and 25 mm, respectively. Compounds 2, 3, 5 did not show antibacterial activity. Taxiresinol (2) showed moderate antifungal activity against *Trichophyton longifusus*, *Microsporum canis*, and *Fusarium solani*. 3-Demethylisolariciresinol (5) exhibited good activity against *T. longifusus*. The chloroform-soluble extract of *T. baccata* displayed moderate antifungal activity against *T. longifusus* and *M. canis*. Compound 3 gave no inhibition against all strains. Lignan derivatives (1 - 5) were also investigated for their *in vitro* cytotoxicity against the Oncology Cell Line Panel (breast, colon, ovary, prostate, lung, and a normal adult bovine aortic

endothelial cell line). Neither of the compounds demonstrated much cytotoxic potency, as the average $IC_{50}$ value for the 9 cells lines was >60 µM. All compounds did not demonstrate much cytotoxic potency according to the reference drug etoposide (Erdemoglu et al., 2004b).

In continuation of our studies on screening of lignans obtained from *T. baccata*, these lignans (1 - 5) were evaluated for their acetylcholinesterase (AChE), butyrylcholinesterase (BChE) and lipoxygenase (LOX) inhibitory activities, which play a role in the pathogenesis of Alzheimer's disease (AD), by *in vitro* spectrophotometric methods, while they were also screened for their antioxidant capacity in 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, ferrous ion-chelating effect, and ferric-reducing antioxidant power (FRAP) tests at 125, 250, 500, and 1000 µg/ml. All compounds exhibited a moderate inhibition against both BChE and LOX, whereas they were inactive towards AChE. Among the tested compounds; 3'-demethylisolariciresinol-9'-hydroxyisopropylether (3) possessed the highest inhibitory activity against both BChE and LOX with $IC_{50}$ values of 86.0 ± 0.2 and 161.0 ± 3.6, respectively. The compounds displayed a great scavenging activity against DPPH especially at 500 and 1000 µg/ml. Besides, they were found to exert noteworthy reducing antioxidant power on ferric ion. In particular, FRAP of compounds 2 (3.552 ± 0.02), 4 (3.021 ± 0.71), and 5 (3.533 ± 0.01) were as high as the reference chlorogenic acid (3.618 ± 0.01) at 1000 µg/ml. None of the compounds exhibited chelating ability against ferrous ion (Kucukboyaci et al., 2009).

## CONCLUSION

In conclusion, various biological activities of the isolated lignans (1 - 5) from *T. baccata* growing in Turkey are summarized in this review. These lignans exerted diverse biological activities against tested methods to some extents. They were found to possess a high activity especially in the anti-inflammatory, antinociceptive, anti-ulcerogenic, antifungal and enzyme inhibitory properties. These lignans (1 - 5) which should be further evaluated to develop safe agents to introduce in modern therapy. Further studies should be made to reveal the mode-action of lignans which might be helpful in understanding the possible roles in human physiology.

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