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Review Article

Anticancer butanolides and lignans from the Makko tree, *Machilus thunbergii* Siebold & Zucc. (Lauraceae). A review

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ABSTRACT

The plant *Machilus thunbergii* Siebold & Zucc., known as Makko tree, is distributed in many countries of south Asia: China, Taiwan, Japan, South Korea, Philippines, Vietnam, Cambodia, Laos. The bark of the tree is used for the preparation of incense powder, and the wood is exploited locally. A few applications of the plant in Chinese and Korean traditional medicines have been mentioned, for the treatment of headache, apoplexy, and dyspepsia. This review provides a survey of the main butanolides and neolignans isolated from the bark and leaves of Makko tree, with a focus on anti-inflammatory, antioxidant, and anticancer compounds. The molecular targets of selected butanolides such as litsenolides A2 and obtusilactone B, and different lignans, including machilins A-I, are discussed. The targeting of lactate dehydrogenase A (LDHA) by machilin A is at the origin of anticancer properties. The review highlights the structural diversity and properties of the machilins.

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1. Introduction

The genus *Machilus* refers to a large group of plants belonging to the Lauraceae family, a major family of flowering plants in the plant kingdom of angiosperms. As reported in the internet database www.theplantlist.org, the genus *Machilus* comprises 95 taxonomically accepted species, while 71 additional plant names are now in synonymy or have even been moved as synonyms to other genera of the Lauraceae family, namely to Persea, *Cinnamomum*, *Phoebe*, *Nothaphoebe*, *Alseodaphne*, *Actinodaphne*, *Dehaasia* and *Litsea*. Furthermore, 72 so-called "unresolved" plant names have not yet received a status of either 'accepted' or 'synonym'. Plants of the genus *Machilus* are evergreen shrubs or trees, largely distributed throughout Asia, essentially in temperate and subtropical areas, and in tropical forests. These woody plants are relatively common. Different species can be found in Cambodia, Vietnam, Malaysia, Laos, Indonesia and Japan (Song et al., 2015; Yahara et al., 2016). There are more than 80 *Machilus* species in China, including about 60 endemic species (Wei and van der Werff, 2008; Mase et al., 2020). One of the common *Machilus* species often found and planted in southeast Asia is *M. thunbergii* Siebold & Zucc. (Fig. 1). The plant was first described by PFB von Siebold and JG Zuccarini in 1846. Notably, the species *Machilus thunbergii* received the second part of its binominal name after the Swedish botanist and physician Carl Peter Thunberg (1743-1828). In Japan, *M. thunbergii* is called the "Japanese bay tree" or "Tabu-No-Ki tree". The bark of the timber tree is used to make a specific incense powder, known as Makko, hence the name Makko tree (Kim, 2012). *M. thunbergii* is an evergreen laurel tree with broad leaves and hermaphroditic (heterodichogamous) flowers

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Fig. 1. The Makko tree (*Machilus thunbergii* Siebold & Zucc.). There are several synonyms for this plant, such as *Persea thunbergii* (Siebold & Zucc.) Kosterm. and *Machilus arisanensis* (Hayata) Hayata. The Makko tree is known as *tabu-no-ki* in Japan, *hóng nán* in China, and *Hu-bak-na-mu* in Korea.

blooming from April to June. This insect-pollinated tree grows to about 15-20 m in height. The fruits - mature from June to August and attractive to some species of bird - are green to black, globular, and about 10 mm in diameter. The plant prefers moist, fertile, well-drained soils, and tolerates a wide range in its pH. It is well represented around coastal areas of Japan, with some fragmented inland populations, mainly around Lake Biwa (Watanabe et al., 2014, 2016, 2018). In Korea, the tree is quite densely distributed. There, the cortex of the plant is used in folk medicine for the treatment of leg oedema, abdominal distension, and pain (Chung, 2000). The tree can be found also in Ryuku Japanese islands, Taiwan, and the Philippines (Wu et al., 2006). *M. thunbergii* is an endangered tree species in eastern China, listed as a third-class state-protected rare tree species, known as *hóng nán* (Xie, 2005; Liu et al., 2013). Species are mainly concentrated in the eastern subtropical part of China (Wuyi, Luoxiao, and Xuefeng Mountains, Nanling and east of Taiwan Mountains). Predictive studies have estimated that climate change will likely affect the distribution of the plant (Yun et al., 2011; Ren et al., 2020). Different fungal pathogens have been inventoried for this plant, such as *Neofusicoccum parvum* and *Lasiodiplodia gilanensis* responsible for leave spot diseases (Li et al., 2018; Choi et al., 2021). *M. thunbergii* Siebold & Zucc. has long been used for the isolation of natural products of potential interest in medicine, the cosmetic sector and food industry. The tree is used in the wood industry and woody wastes may be used to produce sugar (Toyama and Ogawa, 1975). Extracts of the cortex can be used in the textile industry, as natural dyeing of silk fabrics, providing various brown shades (Hand and Lee, 2010). Extracts of the bark can be used in cosmetic preparations, notably in skin whitening products (Son et al., 2003; Uk et al., 2003). There are also diverse uses of the plant for medicinal purposes. The Korean traditional medicine (called *HooBaklp*) uses the leaves of *M. thunbergii* (called *Hu-bak-na-mu* in Korea) to treat headache, apoplexy and dyspepsia, the latter going along with abdominal pain, bloating and nausea (Bae et al., 2010; Korea National Arboretum, 2015). Interestingly, the same medical application was also reported from Chinese traditional medicine (called '*Hoo Bak*') (Park and Namba, 1994). Diverse compounds endowed with anti-inflammatory, antioxidant, anti-bacterial, anti-parasitic, and/or anticancer properties have been isolated from *M. thunbergii*. In this survey, we report on compounds of medicinal interest isolated from *M. thunbergii,* with a focus on anticancer butanolides and lignans. Particularly, a small group of (neo)ligans called "machilins" will display the centre of chemical and bioactivity consideration.

2. Phytochemical analysis of *Machilus thunbergii*

Since the mid-1960s, several phytochemical studies have been performed on *M. thunbergii* to identify bioactive compounds. The first alkaloids were reported in 1964, such as N-norarmepavine isolated from the roots of the plant (Tomita et al., 1964) and since this date, many compounds have been isolated from the roots, leaves or the bark of the tree. The isolation of flavonol glycosides, such as afzelin, guaijaverin and rutin was reported in 1990, from the leaves of the plant, as well as the flavonoids quercetin, quercitrin (quercetin 3-*O*-α-L-rhamnopyranoside) and trifolin (kaempferol 3-*O*-α-D-galactopyranoside) (Park et al., 1990a, 1990b; Kim and Park, 1993). Additional studies led to the isolation of isoquercitrin and hyperin from the leaves of the plant after fractionation with different solvents and column chromatography (Park et al., 1991). The plant contains alkaloids and flavonoids, but it is essentially known for its important content in lignans and neolignans (Fig. 2), particularly abundant in Lauraceae in general (Li et al., 2018). The first lignan derivatives from *M. thunbergii* were characterized in 1987 and designated machilin A-E, co-identified with licarins A and B, the important lignan meso-dihydroguaiaretic acid, (MDGA, occasionally misspelled dihydroguaretic

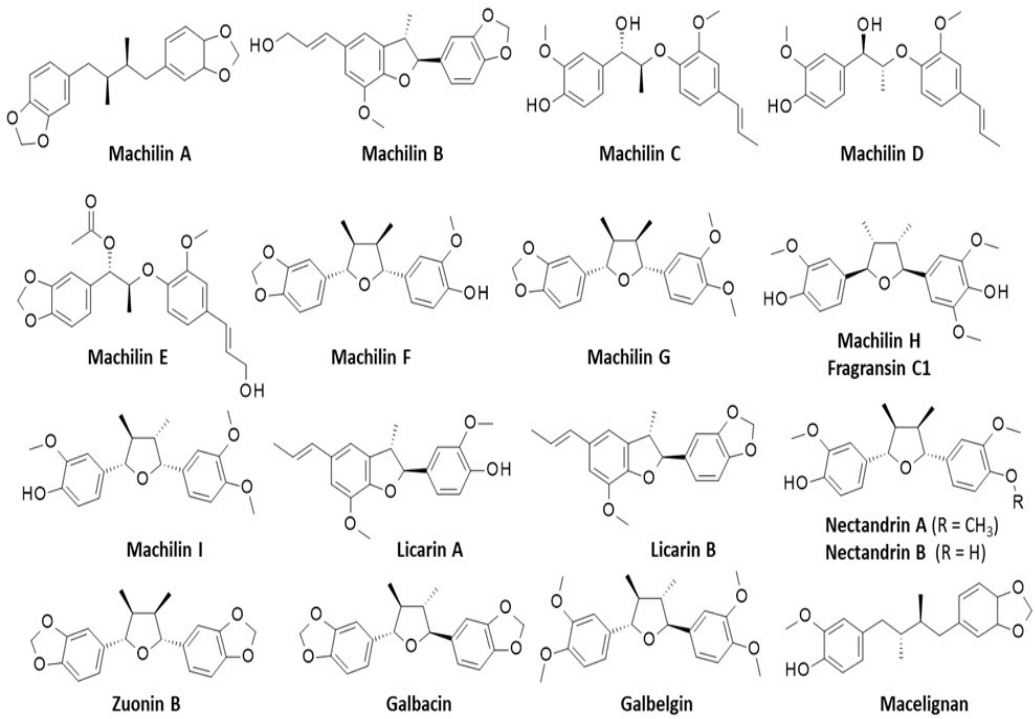

Fig. 2. A selected set of neolignans isolated from *M. thunbergii*. The structures of all machilins are indicated, together with a few related compounds.

acid) (Shinomura et al., 1987). Later, the neolignans machilin F-I were isolated from the bark, together with nectandrins A and B (Shinomura et al., 1988). Derivatives of MDGA have been isolated from the stem bark and characterized, such as (+)-guaiacin, isoguaiacin, isoguaiacin dimethylether, and monomethyl-MDGA (Ryu et al., 2003; Ma et al., 2004). The latter guaiacin-type compounds, and in particular isoguaiacin dimethylether, have revealed an interesting capacity to stimulate osteoblast differentiation, not observed with MDGA (Lee et al., 2007). MDGA is a precursor for the synthesis of methylated and acetylated derivatives with a reinforced anti-inflammatory profile (Choi and Rho, 2017). Successive phytochemical analyses of bark extracts afforded the following lignans or flavans: zuonin B, macelignan, oleiferin C, erythro-austrobailignan-6, (+)-galbacin, (-)-acuminatin, (-)-sesamin, galbelgin and a few dihydrobenzofuran derivatives (Lee et al., 2004a; Park et al., 2004; Li et al., 2004). An extraction of the bark of *M. thunbergii* with dichloromethane afforded more hydrophobic compounds, such as (+)-9'-hydroxygalbelgin, and isogalcatin B and (Ma et al., 2009). *M. thunbergii* is a solid reservoir of bioactive products. Predominantly a series of butanolides and lignans have attracted significant interest due to their antioxidant, anti-inflammatory and anticancer properties and are presented in the following subsections.

2.1. Butanolides from *M. thunbergia*

Two types of butanolides have been isolated from *M. thunbergii*, namely obtusilactone B and litsenolides (Fig. 3a). These compounds are characterized by the

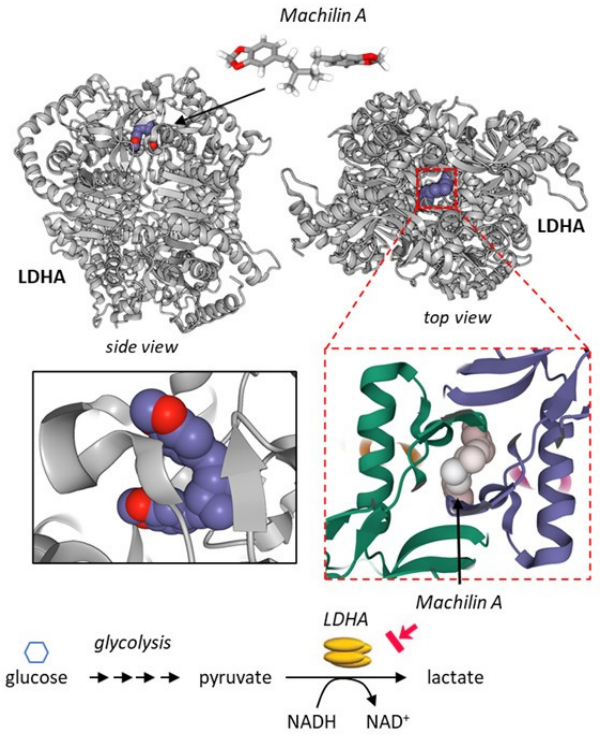

Fig. 3. Machilin A bound to lactate dehydrogenase A (LDHA). The compound deeply inserts between two monomers of the tetrameric protein (PDB code 5ZJF) inducing conformational changes of the active site. Machilin A blocks LDHA into an inactive conformation, suppressing the interaction with the cofactor NADH (Chung et al., 2019).

presence of a γ-butyrolactone moiety substituted with a long alkyl chain. These types of products are abundant in nature. γ-Butyrolactones constitute up to about 10% of all known compounds of natural origin (Kunzmann et al., 2011; Quintana and Estévez, 2018; Hur et al., 2021). Many of these molecules bear a highly reactive α-methylene-β-lactone, susceptible to form adducts with proteins (Kunzmann et al., 2011), leading in some cases to allergic contact dermatitis (Lepoittevin et al., 2009). Obtusilactone B is a typical butanolide isolated from a *n*-hexane extract of the stem of *M. thunbergii*. In this case, the plant sample originated from the city of Pohang, in Korea (Kim et al., 2013). The name obtusilactone came from the plant name *Lindera obtusiloba* Blume (Dankbbai in Japanese), a member of another genus of the Lauraceae family, from which it was isolated for the first time (Niwa et al., 1975a) together with the related compounds isoobtusilactone, obtusilactone A and isoobtusilactone A, all bearing the α-methylene-γ-butyrolactone ring (Niwa et al., 1975b). *L. obtusiloba* Blume contains compounds with a C17 or a C21 chain and some dimers. Obtusilactone B (Fig. 3a) and isoobtusilactone B are C21 derivatives both isolated form *L. obtusiloba* (Niwa et al., 1975c). Obtusilactone B was later isolated from *M. thunbergii*. Obtusilactones display marked anticancer properties. Obtusilactone A is an inhibitor of the human mitochondrial Lon protease, which is frequently upregulated in non-small-cell lung cancer (NSCLC) cell lines. The compound down-regulates expression of the Lon protein, and triggers caspase-mediated apoptosis (Wang et al., 2010). The compound also displays osteogenic effects. It can stimulate new bone formation by bone marrow-derived mesenchymal stem cells (Lin et al., 2017). Obtusilactone B was found to target the barrier-to-autointegration factor (BAF) protein, thereby suppressing phosphorylation of BAF by the vaccinia-related kinase 1 (VRK1) (Kim et al., 2013). By doing so, obtusilactone B inhibits the disruption of the link between DNA and the nuclear envelop, thus blocking the cell cycle progression of cancer cells and inducing tumor cell death. A direct interaction between obtusilactone B and the BAF protein (purified and immobilized on a chip) has been evidenced and an affinity constant (K_D) of 1.39 µM was calculated. A molecular modeling analysis has suggested that the heterocyclic moiety of the natural product is important for the interaction with the protein, in a glycine-rich groove. The predicted drug binding site overlaps with the DNA-binding site of BAF (Fig. 3b). Upon blockade of BAF, the compound traps the protein in the nucleus and prevents its translocation into the cytosol, thereby inhibiting its phosphorylation by VRK1 and the subsequent cellular processes (Kim et al., 2013). Due to above remarkable studies, we recommend further research on the pharmacologic potential of this natural product. From recent research it was reported that the chromatin-associated protein BAF is implicated in post-mitotic nuclear envelope reformation and cytosolic viral regulation (Halfmann and Roux, 2021). It should be noted that BAF inhibitors are actively searched (Burger et al., 2020). For future projects, obtusilactone B could be considered as an archetype for the design of novel BAF-regulatory agents. The other three butanolides identified from the stem bark of *M. thunbergii* are litsenolides A2, B1 and B2 (Fig. 3a). In contrast to obtusilactone B, these three compounds bear a methyl (not methylene) in the alpha position to the lactone, and they differ by the nature of the C-12 alkyl side chain. All three compounds bear the same β-hydroxy-γ-methyl-α,β-unsaturated lactone ring. They were first isolated from *Litsea japonica* which also belongs to the Lauraceae family (Takeda et al., 1972) and later characterized as anti-inflammatory compounds. An ether fraction from an extract of *M. thunbergii* was found to potently inhibit the production of nitric oxide (NO) from lipopolysaccharide (LPS)-induced macrophages (Ryu et al., 2003). A parallel study has identified litsenolides A2, B1 and B2 as the main inhibitors of NO synthesis in activated RAW 264.7 cells. Litsenolides A2 and B1 (IC_{50} = 3.36 and 3.70 µM, respectively) are more potent than litsenolide B2 (IC_{50} = 6.19 µM) as NO synthesis inhibitors. The cellular study indicated that litsenolide A2 suppressed iNOS induction rather than directly inhibiting the enzymatic action of NOS (Kim and Ryu, 2003). These compounds are potent anti-inflammatory agents, capable of inhibiting the production of multiple pro-inflammatory cytokines (iNOS, NO, COX2, PGE2) in activated macrophages *in vitro* and to inhibit the expression of the transcription factor NFκB and the phosphorylated proteins MAPK ERK, JNK, and p38 (Ham et al., 2015, 2017). These effects are entirely consistent with the suppression of NFκB and p38 MAPK activation reported with an extract of *Machilus thunbergii* (Wu et al., 2015). Litsenolides can be found in different species of the Lauraceae family (Chang et al., 2008).

2.2. Lignans from *M. thunbergii*

Guaiaretic acid, dihydroguaiaretic acid and nordihydroguaiaretic acid are 1,4-diarylbutane derivatives, a small group of lignans initially isolated from the resin of *Guaiacum officinale* L. (Fig. 4). Nordihydroguaiaretic acid (NDGA) can be found in the resinous exudates of many plants. This compound is known since a long time, already considered as a molecule with "wide commercial use as an antioxidant" in 1955 (Hearon and MacGregor, 1955), ten years after its first isolation (Waller and Gisvold, 1945) and almost forty years after its first synthesis at the beginning of the twentieth century (Schröter et al., 1918). NDGA can be found in many plants but it is particularly abundant in the desert shrub *Larrea tridentata* (Sessé & Moc. ex DC.) Coville (Zygophyllaceae) widely distributed throughout the arid regions of the southwestern US and northern Mexico. It is commonly isolated from the leaves of this Creosote bush (known as "chaparral"), occurring as a *meso* compound and for this reason it is also called *meso*-nordihydroguaiaretic acid, not to be confused with *meso*-dihydroguaiaretic acid (MDGA) (Arteaga et al. 2005). NDGA is unstable at basic pH, it can undergo spontaneous oxidation in alkaline solution (Billinsky

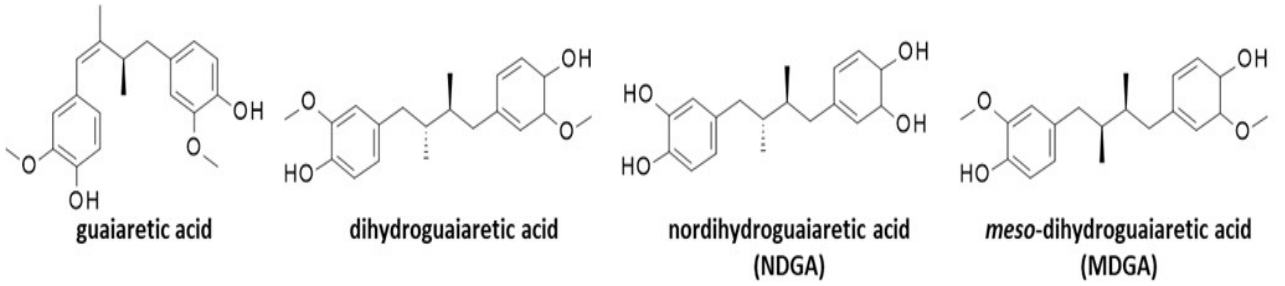

Fig. 4. Chemical structures of guaiaretic acid and its dihydro derivatives.

and Krol, 2008). Various total syntheses of the product and its isomers have been reported (Gezginci and Timmermann, 2001; Son et al., 2005; Xia et al., 2008, 2010). MDGA is used in traditional medicine in Mexico for the treatment of multiple diseases and conditions, including rheumatism, arthritis, diabetes, pain, inflammation, and many others (Lü et al., 2010; Mala John et al., 2020; Manda et al., 2020). With its two catechol rings, MDGA is a potent scavenger of reactive oxygen species (ROS) conferring a robust antioxidant activity. It is also a good anti-inflammatory agent, inhibiting lipoxygenases and activating the transcription factor NRF2 (Nuclear Factor Erythroid 2-related Factor). In the 1940-60s, the compound was largely used in the food industry - notably to prevent oxidation of butter and other food products - until 1968 when it was removed from the Food and Drug Administration's Generally Regarded as Safe (GRAS) list after reports of nephrotoxicity (Lambert et al., 2004). In September 1992, the FDA approved the use of a topical formulation of MDGA (masoprocol, Actinex®, Chemex Pharmaceuticals, Denver, USA) for the treatment of actinic keratosis. However, the drug was withdrawn from market shortly after, due to reports of skin hypersensitivity in rodent experimental models (Olsen et al., 1991; Kulp-Shorten et al., 1993). In humans, cases of allergic contact dermatitis to MDGA have been reported (Epstein, 1997). MDGA has been isolated from of *M. thunbergii* together with a series of structurally related machilin lignans (Fig. 2). These compounds exert variable effects depending on the cell types. With non-tumoral cells, MDGA exerts marked cytoprotective effects, linked mainly to its antioxidant capacity. For example, MDGA was found to protect from the neurotoxic effects of glutamate or staurosporine in primary cultures of rat cortical cells (Ma et al., 2005, 2006). It also protects keratinocytes from ultraviolet-induced damage (Moon and Chung, 2005). Moreover, in asthma model, its anti-inflammatory action was shown to be useful to attenuate airway inflammation and mucus hypersecretion (Song et al., 2016). At the same time, the compound can reduce proliferation of tumoral cells and induce their apoptotic cell death. MDGA has been found to exert anti-proliferative and pro-apoptotic activities toward a diversity of cancer cell types, such as breast cancer cells (Choi et al., 2015), liver cancer cells (Park et al., 2005) and other cell types (Park et al., 1998; Jeong et al., 2015). The cell-type dependent, paradoxical cellular effects of MDGA have been perfectly summarized in different reviews (Hernández-Damián et al., 2014; Mala John et al., 2020; Manda et al., 2020). In addition, MDGA displays interesting antibacterial and antifungal properties (Clemente-Soto et al., 2014; Reyes-Melo et al., 2017). Altogether, the many potential benefits of MDGA have encouraged the design of analogues with reinforced antimicrobial and/or anticancer effects (Reyes-Melo et al., 2017; Nishiwaki et al., 2017). As mentioned above, the machilins are lignans and neolignans initially isolated from *M. thunbergii*. There are nine machilin compounds, named A to I (Fig. 2), but only three of them have been investigated in more detail, which are machilins A, D and G. Machilin A (2,3-dimethyl-1,4-dipiperonylbutane) bears two 1,3-benzodioxole rings in place of the two gaïacol (2-methoxyphenol) moieties of MDGA. This structural change has considerable effects on the activity of the molecule. Machilin A was found to be thirty times more active than MDGA (IC_{50} = 1.6 10-8 vs 4.8 10-7 M) at inhibiting the incorporation of tritiated thymidine into mitogen-stimulated human peripheral-blood lymphocytes. In this *in vitro* cell system, inhibition of DNA synthesis was more pronounced with machilin A than with the reference immunosuppressive glucocorticoid prednisolone (Hirano et al., 1991). In HL-60 leukemia cells, machilin A efficiently inhibited DNA, RNA and protein synthesis leading to marked cytostatic, but not cytotoxic effects (Hirano et al., 1994; Park et al., 2004). Its antioxidant capacity and neuroprotective activity are reduced compared to MDGA, which is not surprising due to the lack of phenol moiety (Yu et al., 2000; Ma et al., 2004). Both compounds were found to be weakly or non-cytotoxic toward HT-29 human colon carcinoma cells and MCF-7 human breast carcinoma cells *in vitro*, with IC_{50} > 45 (HT-29) and 100 (MCF-7) μM (Li et al., 2004). Machilin A behaves as an inhibitor of phospholipase Cγ1, inhibiting the enzyme PLCγ1 more potently than machilin G (IC_{50} = 8.8 and 18.5 μM for machilins A and G, respectively), but machilin G presents a higher cytotoxic potential than machilin A, at least against A549 and MCF-7 cancer cells (Lee et al., 2004). Machilin A is a cell-protective compound, capable of stimulating osteoblast differentiation *in vitro*, via an activation of the p38 MAP kinase pathway (Lee et al., 2009). Importantly, a recent study revealed that the compound

binds to the active site of the enzyme lactate dehydrogenase A (LDHA) and inhibits its activity (Fig. 5) (Chung et al., 2019).

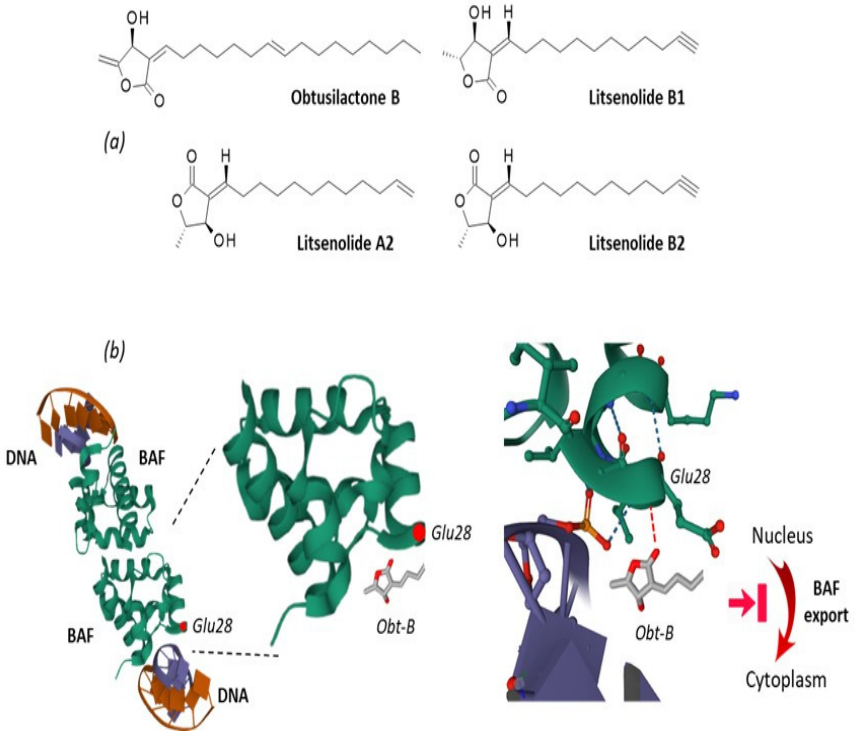

Fig. 5. (a) Structures of obtusilactone B (Obt-B) and litsenolides. (b) Mechanism of action of Obt-B. The barrier-to-autointegration factor (BAF) is bound to DNA (PDB code 2BZF). Obt-B interacts with BAF, via a key residue Glu28, in a glycine-rich region important for DNA binding. Obt-B traps BAF in the nucleus, preventing its translocation into the cytosol and subsequent phosphorylation (Kim et al., 2013).

LDHA is a key enzyme implicated in different metabolic processes, notably in the aerobic glycolytic pathway of cancer cells. The inhibitory potency of machilin A toward LDHA is relatively modest at first sight, with IC_{50} values in the 48-129 µM range depending on cell types, but the effect is sufficient to lead to a marked inhibition of tumor growth *in vivo*, in mice with xenografted CT26 colon tumors after daily administration of machilin A (intraperitoneally at 50 mg/kg). Machilin A behaves as a competitive blocker of NAD (nicotinamide adenine dinucleotide), binding to the active site of LDHA (K_D = 29 µM) and blocking the enzyme into an inactive conformation. This blockade strongly reduces production and secretion of lactate by cancer cells under hypoxic conditions. Drug-induced inhibition of the LDHA activity leads to the production of ROS and triggers apoptosis of cancer cells. Moreover, the suppression of lactate production inhibits M2-like phenotype polarization of macrophages and activated endothelial cells for angiogenesis. These different effects contribute to the anticancer activity of machilin A (Chung et al., 2019). This important discovery should stimulate the search for other anticancer agents in this chemical series. For example, it would be interesting to evaluate the anticancer potential of the natural product saururin A (from Saururus chinensis Baill. (Saururaceae)) which is a hydroxylated derivative of machilin A (Ahn et al., 2001).

Machilin D is structurally distinct from machilin A. It is an 8,4'-oxyneolignan, abundant in the aforementioned plant Saururus chinensis but also found in *M. thunbergii* (Shinomura et al., 1987) and a few other species (Table 1). It is structurally close to other 8-*O*-4′-type neolignans such as machilin C (Xia and Wang, 2010), machilin F, virolin, myrifralignans and surinamensin (Rye and Barker, 2013; Cao et al., 2015). Interestingly, machilin D also displays marked antioxidant and anticancer properties (Lee et al., 2004b). It strongly inhibits NO production in activated RAW264.7 macrophages (Cao et al., 2015) and reduces the growth of breast cancer cells and mammosphere formation, via the blockade of interleukins IL-6 and IL-8 signaling (Zhen et al., 2020). As for machilin A, the compound is not super potent *in vitro* at repressing cancer cell proliferation, but it robustly inhibits cancer cell migration and invasion. Its antitumor activity has been well characterized in an MDA-MB-231 murine model of breast cancer. Machilin D (10 mg/kg) clearly reduced tumor growth, with a selective effect toward aggressive cells with a breast cancer stem cell (CSC) phenotype ($CD44^{high}$/$CD24^{low}$ and aldehyde dehydrogenase (ALDH) positive cells). The combined action of machilin D on the NFκB-dependent cell survival pathway and on CSC leads to the observed anticancer effects *in vivo* (Zhen et al., 2020). Machilin G is a neolignan with a central tetrahydrofuran ring (Fig. 2). It is found in different *Magnolia* and *Nectandra* species, as well as *M. thunbergii* (Table 1). Tetrahydrofuran neolignans are well represented in

Table 1
Plants containing machilins.[a]

Compounds	Plants	Families	References
Machilin A	*Myristica fragrans* Houtt. *Schisandra bicolor* Cheng. *Myristica hypargyraea* A. Gray *Iryanthera lancifolia* Ducke	Myristicaceae Schisandraceae Myristicaceae *Iryanthera*	Chen et al., 2013 Houdkova et al., 2021 Lee et al., 2009 Mesa-Siverio et al., 2008
Machilin B	*(*)*		Chang and Chen, 2016
Machilin C	*Machilus obovatifolia* *Iryanthera ulei* Warb. *Leucas aspera* (Willd.) Link	Lauraceae *Iryanthera* Leucas	Bernal and Suárez, 2009 Chang and Chen, 2016 Sadhu et al., 2003
Machilin D	*Saururus chinensis* (Lour.) Baill. *Piper pleiocarpum* Chang ex Tseng *Jatropha curcas* linn	Saururaceae Saururaceae Euphorbiaceae	Sung et al., 2001 Su et al., 2021 Xu and Tan, 2012
Machilin E	*(*)*		
Machilin F	*Myristica fragrans Houtt.*	Myristicaceae	Lee et al., 2009
Machilin G	*Piper wightii.* *Piper futokadsura Seib. et Zucc.* *Magnolia fraseri Walter.* *Magnolia denudata Desr.* *Schisandra chinensis (Turcz.) Baill.* *Nectandra megapotamica (Spreng) Chodat et Hassler*	Piperaceae Piperaceae Magnoliaceae Magnoliaceae Schisandraceae Lauraceae	da Silva Filho et al., 2008 Konishi et al., 2005 Noshita et al., 2008 Prasad et al., 1994 Schühly et al., 2010 Zhang et al., 2013
Machilin H[b]	*Myristica fragrans* Houtt.	Myristicaceae	Hattori et al., 1987
Machilin I	*Machilius odoratissima* Nees *Machilus robusta* W.W.Sm. *Nectandra megapotamica* (Spreng.) Mez. *Acorus tatarinowii* Schott	Lauraceae Lauraceae Lauraceae Araceae	Bu et al., 2013 Lu et al., 2016 Phan et al., 2006 Ponci et al., 2015

[a]All machilin compounds (A-I) have been isolated initially from *Machillus thunbergii* Siebold & Zucc. (Shinomura et al., 1987, 1988). The table indicates only other plants from which a given machilin compound has been isolated and identified. (*) Machilins B and E have been isolated from *M. thunbergii* exclusively. bSynonym: (+)-fragransin C1 (PubChem CI: 13870578).

plants, with compounds like arctigenin and many others (He et al., 2018; Cui et al., 2020). 2,5-Diaryl-3,4-dimethyltetrahydrofurans, such as nectandrins A/B also found in *M. thunbergii*, display cell protective effects and neurotrophic activities in some cases (Zhai et al., 2005). The pharmacological characteristics of machilin G are relatively similar to those of machilin A. It is not cytotoxic but presents anti-inflammatory, antioxidant and cell-protective effects (Yu et al., 2000; Noshita et al., 2008; Ponci et al., 2015). Machilin G has been used as a structural basis for the design of antiparasitic agents, via the replacement of the furan ring with other heterocycles, such as triazole and isoxazole (Costa et al., 2016; Cardozo Pinto de Arruda et al., 2019; das Neves et al., 2019; Trefzger et al., 2019). Diaryl-tetrahydrofuran lignans have attracted the attention of chemists (Hazra and Hajra, 2013; Teponno et al., 2016). Chemical efforts led to the synthesis of machilin H, also known as fragransin C1 (from the plant *Myristica fragrans houtt*. (myristicaceae)) and its enantiomer *ent*-fragransin C1 (Chaimanee et al., 2017).

3. Concluding Remarks

Machilus species are well distributed throughout Asia. In south Asia, and India in particular, the most common *Machilus* species are *M. macrantha* Nees, now placed within another genus under the name *Persea macrantha* (Nees) Kosterm. and *Machilus bombycina* King, now taxonomically identified as *Machilus gamblei* King ex Hook. f. (Tatiya et al., 2017). *M. thunbergii* is mainly found in southeast Asia, up to the south of China. There is a mention of the use of resin and bark from this tree to treat oedema and abdominal pain in Korean traditional medicine (Yu et al., 2000) but there is a lack of studies about the traditional use of this plant in general. The bark of the tree is essentially exploited to make incense powder and sticks, the famous Makko, a natural combustible largely used in Asian temples. In addition, essential oils derived from the leaves or the fruits of the *M. thunbergii* have been exploited. They are rich in benzenoids and terpenoids (phellandrene, cymene derivatives) and can be used as insect repellant and antifungal (Nii et al., 1981a, 1981b, 1983). An essential oil from the leaves of a species of *M. thunbergii* collected in Taiwan was found to contain various sesquiterpenoids, such as β-eudesmol and α-humulene, with anti-mildew activity (Su et al., 2015). There are different possibilities to exploit extracts of the plant, including as a skin antioxidant/antiaging product (Uhm et al., 2010).

The Makko tree is also an interesting reservoir of anticancer natural products, in particular butanolides and lignans. This type of chemical composition is not unique to *M. thunbergii* since similar products have been observed in the species *M. wangchiana* (Cheng et al., 2009). The specie *M. japonica* (var. kusanoi (Hayata) J.C. Liao) was found to contain butanolides, named machinolides A-F, structurally related to the litsenolides of *M. thunbergii* (Li et al., 2020). However, the compound obtusilactone B, qualified as a BAF-interacting protein, is unique to the Makko tree (Kim et al., 2013). In addition, the panel of (neo)lignans isolated from this tree is broader than that found in other *Machilus* species. The machilin compounds provide interesting anticancer agents, notably machilins A and D. The recently reported anticancer properties of machilin A *in vivo*, associated with a blockade of the LDHA enzyme (Chung et al., 2019) open a novel perspective for the use of this compound and the plant extracts. Lactate dehydrogenase (LDHA) converts pyruvate to lactate in the final step of glycolysis. The enzyme, often upregulated in cancer, is now viewed as an important anticancer target and novel inhibitors are actively searched, notably for the treatment of osteosarcoma (Fang et al., 2017; Feng et al., 2018; Wang et al., 2020; Woodford et al., 2020). Moreover, recent studies have pointed out the key role of LDHA in osteoarthritis (Li et al., 2020). Binding of LDHA to NADH promotes the production of ROS and induces pro-inflammatory mediators in chondrocytes (Arra et al., 2020). *M. thunbergii* extracts and several lignans, including machilins A and F, have shown stimulatory effects on osteoblast differentiation (Lee et al., 2007, 2009). For these different reasons, the use of Makko extracts can be encouraged, at least to investigate further the potential benefits of this plant in cancer and bone-related diseases.

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Conflict of interest

The author declares that there is no conflict of interest.

Abbreviations

LDHA: Lactate dehydrogenase A; MDGA: Meso-dihydroguaiaretic acid; ROS: Reactive oxygen species.

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