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# *Walsura robusta* Roxb. (Meliaceae), a little-known tree with a rich limonoid profile

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## ABSTRACT

The plant *Walsura robusta* Roxb. (Meliaceae) is a robust tree largely distributed in south-east Asia, including provinces of southern China. A few traditional usages of the plant have been mentioned, notably for the treatment of microbial infections. But experimental studies using different types of plant extracts only revealed modest antibacterial effects, and no major antiparasitic activity. *Walsura robusta* Roxb. is a rich source of secondary metabolites. Several series of limonoids have been isolated from the leaves or the fruits of the plant, such as walsuronoid A-I, walsurins A-E, walsunoids A-I, walrobsins A-R and other cedrelone- or dihydrocedrelone-type limonoids, in addition to a few other terpenoids. All information about *Walsura robusta* Roxb. have been collated in this brief review. The analysis underlines the presence of two limonoids endowed with significant anticancer activities, walsuronoid B and cedrelone. They both activate the production of reactive oxygen species in cancer cells, modulate mitochondrial activities and induce apoptosis of cancer cells. Their molecular targets and mechanism of action are discussed. *Walsura robusta* Roxb. has a potential for the development of anticancer natural products. The use of the plant extracts could be further considered for the treatment of diseases with a cell proliferation component.

**KEY WORDS:** Anticancer agents, limonoids, Meliaceae, natural products, *Walsura robusta*.

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## WALSURA ROBUSTA ROXB.: A ROBUST TREE

The plant genus *Walsura* comprises about 50 different names but there are only 4 accepted specie names: *W. pinnata* Hassk., *W. trichostemon* Miq., *W. villosa* Wall. ex Hiern. and *W. robusta* Roxb (<http://www.theplantlist.org>). There are other commonly used names, such as *W. cochinchinensis* (Baill.) Harms and *W. yunnanensis* C.Y. Wu but they are both synonyms for *Walsura pinnata* Hassk. These plants, belonging to the *Meliaceae* family, are usually found in subtropical regions of Southern China, India, Indonesia, and the Asean member countries.

The specie *Walsura robusta* Roxb. (synonym: *Surwala robusta* (Roxb.) M. Roem.) is an evergreen large tree which can usually grow 20-30 meters tall, with large leaves (Fig. 1). The outer bark is grey-brown whereas the inner bark is pink-red, with a specific wood anatomy. The wood of *W. robusta* presents a much larger vessel pore density (308/sq.mm) than the wood of *W. trifoliolata*, *W. tubulata*, and *W. chrysogyne* (at 81-154/sq.mm). The fruits of *W. robusta* Roxb. are non-edible, in contrast to those of *W. pinnata* Hassk. which are sweet-tasting brown-orange fleshy berries. From a taxonomic point of view, *W. robusta* belongs to a distinct subgroup compared to other *Walsura* species (Clark,

1994). The tree can be found in south-east Asia, notably in Vietnam (where it is called *lông tong*), Cambodia, Thailand, Laos, Myanmar, and Malaysia. There is an old mention that the tree is commonly grown in Chittagong (Ghosh, 1968) and in the Rajkandi reserve forest of Moulvibazar, (Bangladesh) (Haque *et al.*, 2018). There may be confusion about the name of the plant because several studies mention that the vernacular Bengla name for *W. robusta* is in *bonlichu* (or *bonlichu*), whereas other studies refer to *bonlichu* as a totally different tree, *Xerospermum laevigatum* Radlk. (Pasha and Uddi, 2019; Abdullah *et al.*, 2020). *W. robusta* Roxb. is found also in the south of China, notably in the Yunnan, Guangxi, Guangdong, and Hainan provinces (Sakkat, 2007).

## EXTRACTS OF WALSURA ROBUSTA ROXB. AND THEIR USES

There are a few reports mentioning the traditional use of extracts of *W. robusta* Roxb. to treat various diseases and conditions. In Thailand, extracts of the leaves and twigs of the plant (called *bonlichu*) are used to treat microbial infections and diarrhea. In China, it may be named name “*geshesu*” as mentioned in a study (Hou *et al.*, 2013), although it is possible that this Chinese

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**Figure 1:** The plant *Walsura robusta* Roxb. (Meliaceae) and its geographic breakdown. (a) the tree. (b) leaves and fruits (<http://tracuuduoclieu.vn/walsura-robusta-roxb.html>). (c) The plant can be found in Vietnam, Laos, Cambodia, Thailand, Myanmar, Malaysia, Bhutan, Bangladesh, and in provinces of south China (Yunnan, Guangxi, Guangdong, and Hainan) (<http://www.plantsoftheworldonline.org/taxon/urn:lsid:ipni.org:names:579946-1>)

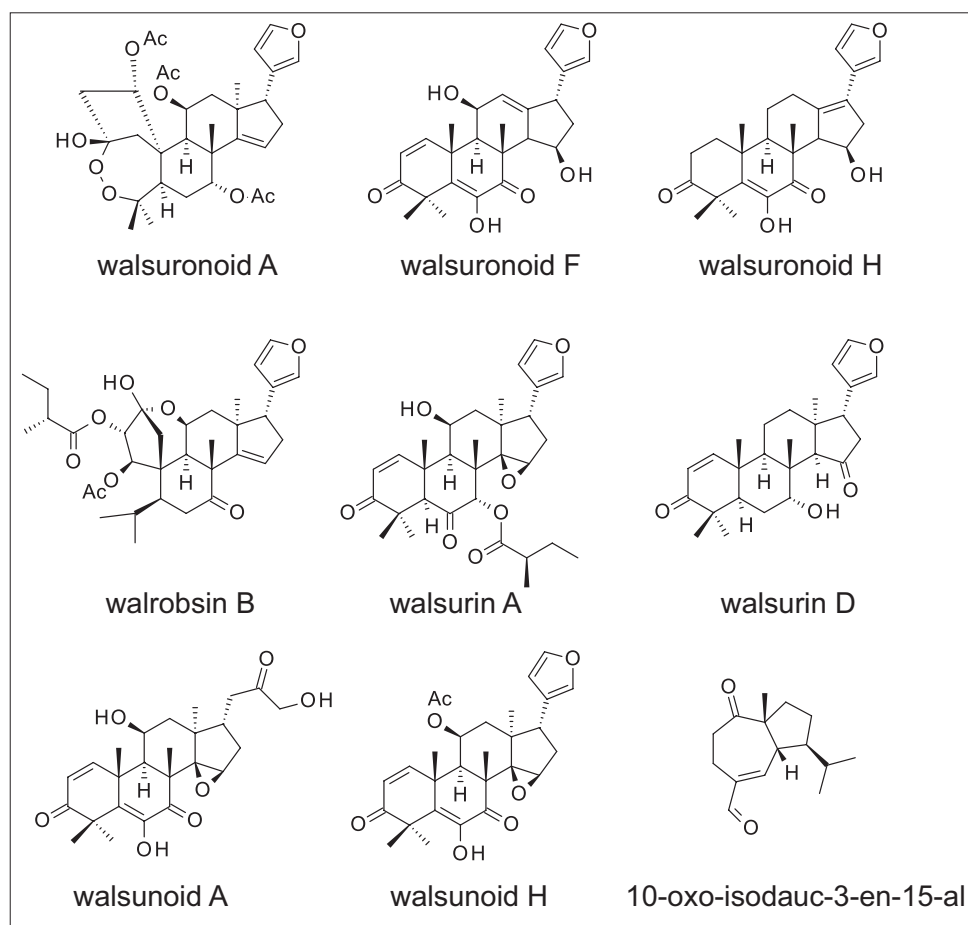
name refers in fact to *W. yunnanensis*, as cited in another study (Luo *et al.*, 2006). *W. robusta* seem to be used in traditional medicine in diverse countries in Asia, but there is a lack of robust information about this traditional usage. Moreover, there is also little experimental evidence to support the traditional medicinal use of *W. robusta*. Initially, a modest antibacterial activity was reported with an ethanolic plant extract found to inhibit the growth of a clinical isolate of methicillin-resistant *Staphylococcus aureus* (MRSA) and the *S. aureus* ATCC strain

25923 with a minimum inhibitory concentration (MIC) of 1.6 mg/ml (Voravuthikunchai and Kitpip, 2005a, 2005b). A better level of activity was observed using wood extracts of the plant against the enterohaemorrhagic *Escherichia coli* strain O157:H7, with MIC of 0.09 and 0.19 mg/ml for the aqueous and ethanolic extracts, respectively (Voravuthikunchai *et al.*, 2004) but a later study reported a marginal bacteriostatic and bactericidal activities with a similar extract (Voravuthikunchai and Limsuwan, 2006). In another study, an aqueous extract of *W. robusta* was found to mildly inhibit the growth of Gram-positive and some Gram-negative bacteria, including *E. coli*. In the same study, the plant extract was tested against trophozoites of the intestinal parasite *Giardia intestinalis* but no anti-giardial activity was observed (Voravuthikunchai *et al.*, 2010). Clearly, there is not enough experimental data to support the traditional use of the plant as an anti-infectious agent.

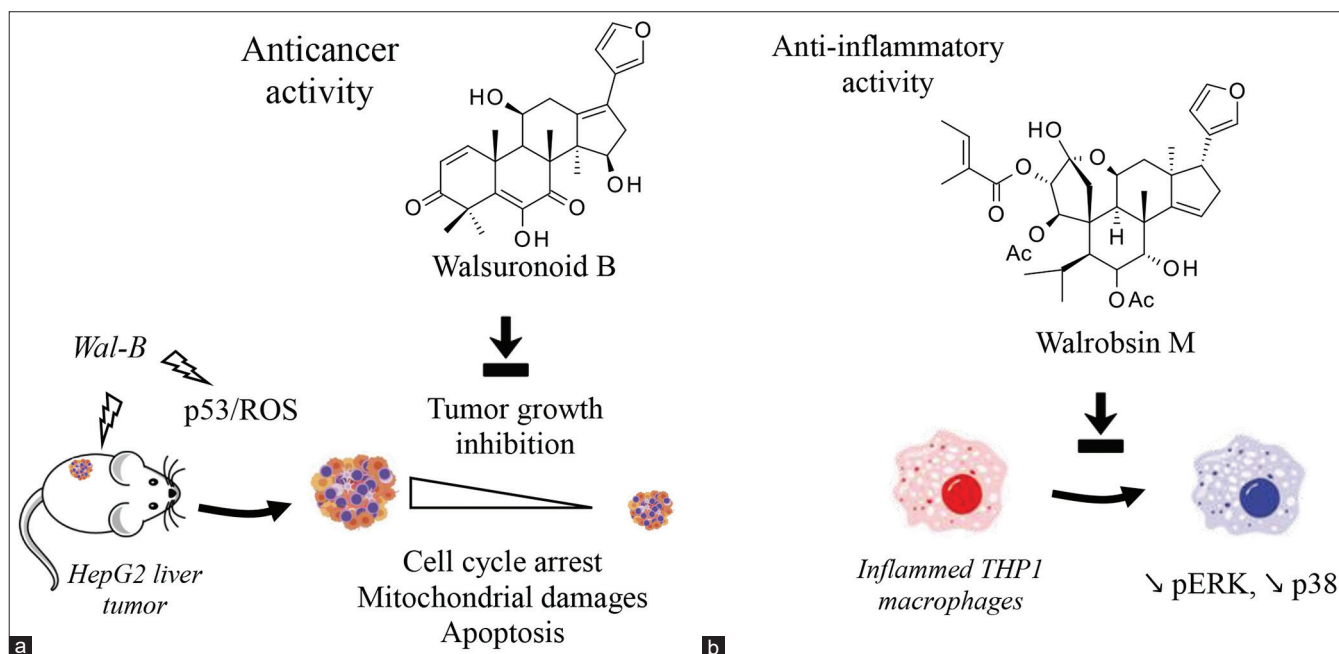
### PHYTOCHEMICAL ANALYSES OF WALSURA ROBUSTA ROXB.

Diverse types of secondary metabolites have been isolated from *W. robusta*, in particular limonoids which are heavily oxygenated, modified triterpenes frequently encountered in Meliaceae and Rutaceae (*Citrus* species) and to a lesser extent in Cneoraceae and Simaroubaceae (Tan and Luo, 2011; Tundis *et al.*, 2014; Zhang and Xu, 2017). The major limonoids in *W. robusta* are named walsuronoids A-C, initially isolated from the leaves of the plant (Yin *et al.*, 2007). Walsuronoid A (Fig. 2) bears a seco limonoid skeleton with a 3,4-peroxide bridge and walsuronoids B and C possess an 18(13→14)-abeo-limonoid skeleton. Walsuronoid C has been considered as an oxidation product of walsuronoid B because its furyl ring is easily oxidized when exposed to air in chloroform. A modest growth inhibition of the malaria parasite *Plasmodium falciparum* was observed with walsuronoids A and B (40% inhibition at the dose of 40  $\mu$ M) (Yin *et al.*, 2007). Walsuronoid B was also identified from the fruits of the plant together with a series of linonoids, known as walsuronoid F-I and walsurins A-E (Fig. 2) and many other terpenoids (Zhang *et al.*, 2017).

Walsuronoid B deserves a special mention because it has been shown to exert potent anticancer effects *in vitro* and *in vivo* (Geng *et al.*, 2017). The compound dose-dependently inhibited the proliferation of several types of cancer cells, with  $IC_{50}$  in the range of 3-4  $\mu$ M. Walsuronoid B blocked cell cycle progression of HepG2 and Bel-7402 liver cancer cells ( $G_2/M$  arrest), with a concomitant up-regulation of cyclin B1 and down-regulation of (phospho)-cdc55C. The compound was found to trigger a massive apoptosis of these malignant cells, with activation of caspases and a drug-induced dysfunction of mitochondria and lysosomes (Fig. 3a). The molecular target of the drug is not known at present, but the compound enhanced the production of reactive oxygen species (ROS) and elevated the expression of the tumor-suppressor protein p53. Interestingly, walsuronoid B (at the intraperitoneal dose of 4 mg/kg) displayed a marked anticancer activity in mice with xenografted HepG2 liver tumors, with an efficacy comparable to that of the standard drug cisplatin (Geng *et al.*, 2017). The activation of the ROS/



**Figure 2:** Chemical structures of selected natural products isolated from *Walsura robusta* Roxb



**Figure 3:** Schematic representation of (a) the anticancer activity of walsuronoid B and (b) the anti-inflammatory action of walrobsin M. Walsuronoid B activates the production of reactive oxygen species (ROS) and the tumor suppressor protein p53, leading to apoptotic cell death (Geng *et al.*, 2017). Walrobsin M represses the expression of the phosphorylated signaling proteins ERK (extracellular signal-regulated kinase) and p38 in THP-1-like macrophages (stimulated with the skin pathogen *Propionibacterium acnes*), thereby inhibiting the MAPK signaling pathway (An *et al.*, 2019)

p53 signaling pathway is central to the mechanism of action of walsuronoid B, as it is the case for other anticancer plant natural products like the cardiac glycoside odoroside A from the plant *Nerium oleander* Linn. (Chen *et al.*, 2019), betulinic acid (Shen *et al.*, 2017) and gambogic acid (Liang and Zhang, 2016) for examples. There is no doubt that walsuronoid B warrants further studies to better define its mode of anticancer action, tumor selectivity and molecular targets.

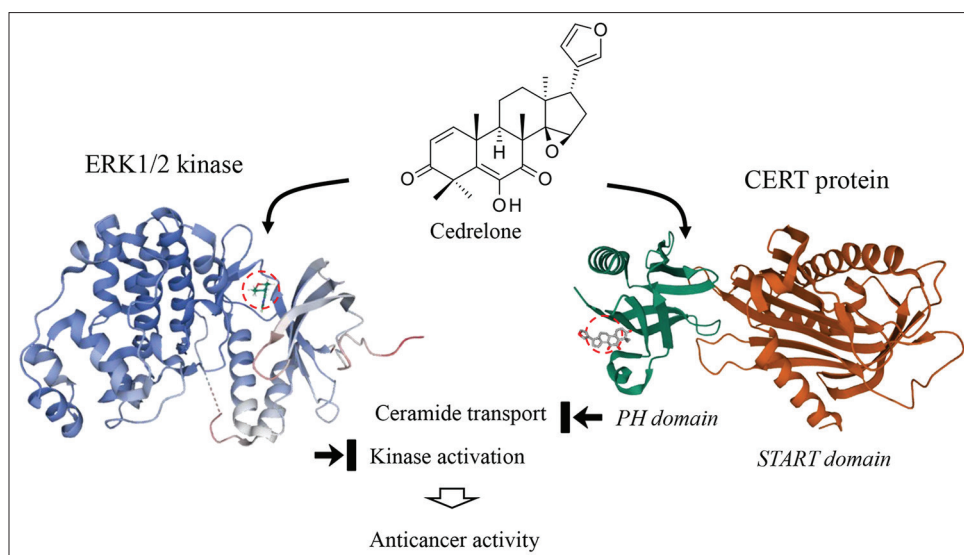
Another small group of limonoids isolated from *W. robusta* has been named walsunoids A-I, isolated together with different cedrelone-type limonoids such as 11 $\beta$ -hydroxyisowalsuranolide and 11 $\beta$ -hydroxydihydrocedrelone (Wang *et al.*, 2016). These compounds were tested against the human 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1), the enzyme which reduces inert cortisone into active cortisol, and which is frequently implicated in metabolic diseases (obesity, diabetes). A modest inhibition of human 11 $\beta$ -HSD1 was observed with walsunoid H (Fig. 2) *in vitro* (IC<sub>50</sub> = 9.9  $\mu$ M) (Wang *et al.*, 2016).

Two other analogues with an atypical 5-oxatricyclo[5.4.1<sup>1,4</sup>]hendecane ring system have been isolated from the root bark of the plant. They were named walrobsins A and B (Fig. 2). These two compounds showed no cytotoxic activity, but a modest anti-inflammatory activity was reported with walrobsin A. The compound was found to inhibit the release of the pro-inflammatory cytokine interleukin-1 $\beta$  from lipopolysaccharide-activated RAW264.7 macrophages and to dose-dependently inhibit the expression of the inducible nitric oxide synthase (iNOS) enzyme, the enzyme responsible for nitric oxide (NO) production (An *et al.*, 2017). A subsequent phytochemical analysis from the root bark of *W. robusta* led to the identification of other compounds with a 5-oxatricyclohendecane ring system and named walrobsins C-to-R (An *et al.*, 2019). The bioactivity of these compounds has not been deeply investigated but a preliminary evaluation indicated that walrobsin M (Fig. 3b) presents an interesting anti-inflammatory profile, with a drug-induced down-regulation of the expression of protein phospho-ERK and phospho-p38 in inflamed THP-1 macrophage cells (An *et al.*, 2019).

The fruits of the plant also contain a series of compounds structurally similar to cedrelone (Fig. 2) and dihydrocedrelone, which were found to potentiate the cytotoxicity of the anticancer drug doxorubicin in human MCF-7/DOX breast cancer cells, normally resistant to the drug. These compounds could efficiently reverse the multidrug resistance (MDR) phenotype *in vitro* (Zhang *et al.*, 2017). Cedrelone limonoids have been isolated from *W. robusta*, *W. yunnanensis* (Ji *et al.*, 2014), *Toona sinensis* (Jiang *et al.*, 2020) and from the leaves of *Trichilia americana*, another plant of the Meliaceae family (Ji *et al.*, 2015). Acetylation of the cedrelone core affords cedrelone acetate, a synthetic molecule presenting enhanced cytotoxic properties and efficient to revert the malignant phenotype of cancer cells (Becceneri *et al.*, 2020). Cedrelone itself is an interesting anticancer agent because this compound was found to activate the expression of the protein PBLD (phenazine biosynthesis-like domain-containing protein) which is often down-regulated in hepatocellular carcinoma (HCC) (Wu

*et al.*, 2019). PBLD functions as a tumor suppressor. An increase of the expression of PBLD could reduce HCC cell growth and invasion via inactivation of several tumorigenesis-related signaling pathways (Li *et al.*, 2016). Through the activation of PBLD in cells, cedrelone regulates the Ras and Ras-proximate-1 (Rap1) signaling pathways and this signaling action triggers apoptosis of cancer cell, while reducing cell proliferation and the epithelial-mesenchymal transition (Wu *et al.*, 2019). The antitumor capacity of cedrelone has been characterized in different experimental models, notably using drug-resistant human glioma cells (Cao *et al.*, 2019) and leukemia cells (Wang *et al.*, 2019). In both cases, the compound selectively affected the ERK/MAPK signaling pathway. A direct interaction of cedrelone with the ERK1 kinase has been postulated, based on a computational docking analysis. The compound was predicted to bind to a small pocket on the protein, leading to the kinase activation (Fig. 4). Similarly, a combination of docking and molecular dynamic simulations has suggested that cedrelone could bind to the multi domain ceramide transfer protein (CERT), a protein implicated in sphingolipid metabolism and which allows the transport of ceramide from the endoplasmic reticulum to the Golgi apparatus (Fig. 4). Cedrelone would bind to the linked PH and START domains of CERT, thereby inhibiting the protein (Ghoula *et al.*, 2020). Inhibition of CERT is considered as an appropriate mechanism to re-sensitize cancer cells to chemotherapy (Palau *et al.*, 2018; Kumagai and Hanada, 2019). The anticancer effects of cedrolone have been evidenced using other cell types, including MDA-MB-231 breast cancer cells, NCI-H460 non-small cell lung cancer cells and A375 melanoma cells (Cazal *et al.*, 2010; Fuzer *et al.*, 2013). Cedrolone is an interesting natural product which also displays anti-fungal and insecticidal activities (Govindachari *et al.*, 1995, 2000). It exhibits a sub-micromolar activity against the protozoan parasite *Cryptosporidium parvum in vitro* (EC<sub>50</sub> = 0.27  $\mu$ M) (Jin *et al.*, 2019) and causes lethal and sublethal effects on the armyworm *Spodoptera frugiperda* (Giongo *et al.*, 2016).

Other terpenes and sesquiterpenes have been isolated from *W. robusta*, such as the carotane sesquiterpene 10-oxo-isodauc-3-en-15-al (Fig. 2) and its nitro derivative, both isolated from a methanolic extract of the plant leaves. These two compounds showed no antimicrobial activity against *Staphylococcus aureus* and different MRSA strains (Hou *et al.*, 2013). It is worth to note that this isodaucane type sesquiterpenoid can also be found in the leaves of the sunflower crop (*Helianthus annuus* L.) and it has revealed a significant herbicidal activity. Indeed, 10-oxo-isodauc-3-en-15-al was found to inhibit coleoptile elongation and is considered as a useful allelopathic compound (Fuentes-Gandara *et al.*, 2019). It has been found in diverse plants, such as *Senecio crassiflorus* (Pox.) De Candolle (Jares and Pomillo, 1989), *Uvaria lucida* (Moriyasu *et al.*, 2012), *Chromolaena laevigata* (Misra *et al.*, 1985) and *Conza linifolia* (Hussein *et al.*, 1995). Surprisingly, this compound and its C-10 epimer which is known as sinulin A, can be found also in a marine organism, the Xisha soft coral *Sinularia* sp. (Qin *et al.*, 2018).



**Figure 4:** Two potential protein targets of the limonoid cedrelone, which can be isolated from *Walsura robusta* Roxb. The molecular model (left) shows a drug fragment bound to the ERK1/2 kinase, to modulate the phosphorylation and catalytic activity of the enzyme (PDB: 6G91) (Heightman *et al.*, 2018). A molecular modeling analysis has predicted that cedrelone can bind to the same site of the protein, thereby activating the kinase (Wang *et al.*, 2019). Molecular modeling has also predicted that cedrelone can bind to the PH domain of the multi domain ceramide transfer protein (CERT) to inhibit its transport activity (Ghoula *et al.*, 2020). Binding of the compound to ERK1/2, CERT and other proteins likely contributes to the anticancer activity of this limonoid

## CONCLUSION

Plants of the *Walsura* genus have been little studied thus far. For examples, the PubMed data bank comprises 30 references with the name *Walsura*, compared to >2000, 300 and 150 for the genera *Trichilia*, *Aglaiia* and *Xylocarpus*, which also belong to the *Meliaceae* family (as of April 2021). Moreover, in the *Walsura* genus, the specie *W. pinnata* Hassk (synonyms: *W. cochinchinensis* (Baill.) Harms and *W. yunmanensis* C.Y. Wu) is more frequently studied than *W. robusta* Roxb. This is perhaps not surprising because the plant is not so frequently used in traditional medicine, except in very local areas. *W. robusta* trees should be investigated further, for the usefulness of their woods and the diversity of the secondary metabolites which can be isolated from the bark, leaves and fruits of the plant.

As presented here, *W. robusta* Roxb. provides a rich reservoir of limonoids, a huge family of natural products widely distributed in nature. Limonoids can be isolated from many plants, and some of them can be (semi) synthesized (Zhang and Xu, 2017; Fu and Liu, 2020). They are particularly abundant in *Meliaceae* (Tan and Luo, 2011). The great majority of the new natural products isolated from *W. robusta* over the past few years are limonoids, such as the walsuronoids, walrobsins, walsurins, and walsunoids. Beyond the isolation and characterization of these compounds, the bioactivity measurements have been limited mainly to a few preliminary *in vitro* tests, notably to evaluate their antimicrobial activity. No outstanding activity has been reported, but occasionally a few compounds revealed a modest antibacterial or anti-inflammatory effect. Two compounds emerge from this literature survey: walsuronoid B and cedrelone, because they both present noticeable anticancer properties against multiple cancer cell lines. Walsuronoid B stands as a

potent anticancer agent active in a xenograft model *in vivo* and cedrelone also displays marked anticancer activities. They both impact mitochondrial activities, cause an increase of ROS in cells, and trigger apoptosis of cancer cells (Geng *et al.*, 2017; Cao *et al.*, 2019). They could be considered as prototypes for the design of novel anticancer derivatives (Becceneri *et al.*, 2020).

Plants of the *Walsura* genus, and the specie *W. robusta* Roxb. in particular, have received little attention thus far. This robust tree, well distributed in south Asia, should be considered further in the search of natural products of medicinal interest. We can certainly recommend the investigation of extracts of the plant and its abundant fruits, for the treatment of cancers, and possibly other diseases with a cell proliferation component. The specie deserves its named “*robusta*”, as a robust provider of bioactive limonoids.

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## DECLARATION OF COMPETING INTEREST

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