Trends Phytochem. Res. 6(4) 2022 282-291

Trends in Phytochemical Research (TPR)

Journal Homepage: http://tpr.iau-shahrood.ac.ir

Original Research Article

The anti-inflammatory and antitumor potential of *Cryptocarya concinna* Hance and its phytoconsituents

Christian Bailly[1,2]✉* And Gerard Vergoten[2]

[1]OncoWitan, Consulting Scientific Office, 59290, Lille (Wasquehal), France
[2]University of Lille, Institut de Chimie Pharmaceutique Albert Lespagnol (ICPAL), Faculté de Pharmacie, 3 rue du Professeur Laguesse, BP-83, F59006, Lille, France

ABSTRACT

The tree *Cryptocarya concinna* Hance is largely distributed in southeast Asia and essentially used for its robust wood. Alcoholic extracts made from the leaves or roots of the plant have revealed anti-inflammatory and anticancer properties. The DNA-damaging dihydrochalcone derivative cryptocaryone accounts for the anti-proliferative and pro-apoptotic activities observed with the extracts. Other bioactive products have been isolated, including α-pyrone derivatives such as cryptoconcatones A-L and flavonoids such as cryptoconones A-E. A structural analogy is underlined between cryptoconcatone D and two known compounds with an α,β-unsaturated δ-lactone: pironetin and the styryl-lactone goniothalamin which targets the peroxisomal protein MFE2 (multifunctional enzyme type2). Pironetin is a potent α-tubulin binder with robust anticancer properties. By analogy, the binding of cryptoconcatone D to the pironetin-site of α-tubulin is proposed. The review shed light on the phytochemical constituents of *Cryptocarya concinna* and the biological properties of α,β-unsaturated lactone compounds isolated from this little studied plant.

ARTICLE HISTORY

Received: 17 October 2022
Revised: 05 December 2022
Accepted: 19 December 2022
ePublished: 27 December 2022

KEYWORDS

Anticancer
Anti-inflammatory
Cryptocarya concinna
Cryptocaryone
Cryptoconcatone
Natural products

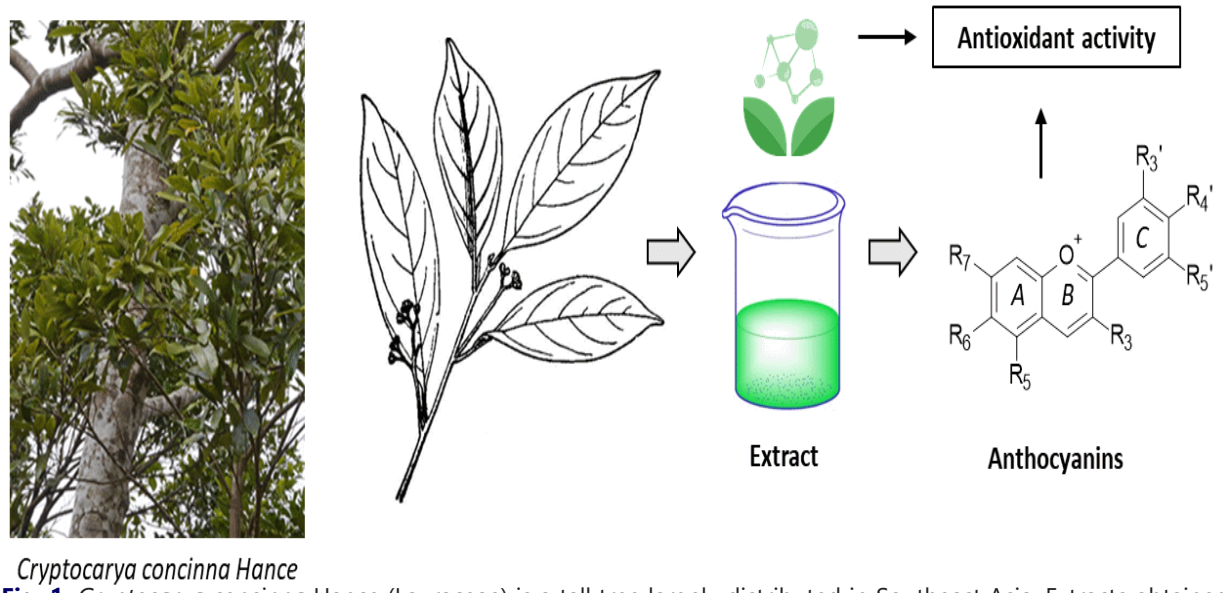
dor: 20.1001.1.25883623.2022.6.4.2.4

1. Introduction

Cryptocarya concinna Hance (Lauraceae) is a tall evergreen tree well distributed in southern China (Guangdong, Guangxi, SE Guizhou, Hainan, Jiangxi). It can be found also in eastern Thailand, Laos, Cambodia, northern Vietnam and Taiwan (de Kok, 2015; Zhang et al., 2020). The tree, which can grow up to 18 meters tall, is harvested from the wild for its tough wood (Fig. 1). It grows usually in low-altitude (550-1200 m) subtropical and tropical forests, in valleys and on low hillsides. The bole can be up to 35cm in diameter (Chudnoff, 1984). The wood is used for housing timber and furniture making. There are 368 species with an accepted name in the *Cryptocarya* genus. *C. concinna* Hance (synonym: *C. lenticellata* Lecomte) is one of them. The plant can be cultivated but the growth volume of *C. concinna* plantation is slow and the growth cycle is long. It is better to rely on the natural regeneration of *C. concinna* plantation which provides sufficient seedlings storage (Wu et al., 2020). However, *C. concinna* trees are quite sensitive to nutrient deficiency and to acid rains which increase the soil content of Mn toxic for the plant (Liu et al., 2007a, 2007b). Apparently, the plant is not used in traditional medicine, although there is an isolated citation of the use of the raw fruits for the treatment of stomachache in Thailand (local name Ma Khuae Jae) (BGO Plant Database). Apart from this unique web citation, there is no study indicating the use of the plant extract for a medicinal purpose. However, there are interesting studies on the isolation of bioactive compounds from the plant. Young leaves of *C. concinna* have been found to contain a large proportion of phenolic compounds, including anthocyanins with marked antioxidant properties. The leave extracts were shown to contain various flavonoids serving as photoprotective agents

✉Corresponding author: Christian Bailly
Tel: +33 622661817; Fax: +33 622661817
E-mail address: christian.bailly@oncowitan.com, **doi: 10.30495/tpr.2022.1970912.1283**

(Zhu et al., 2016; Zhang et al., 2018). The anthocyanins provide a photoprotective effect for young leaves in high-light environments (Yu et al., 2019). Over the past 15 years, diverse bioactive compounds have been isolated from extracts of *C. concinna*, principally flavonoids and α-pyrone derivatives. The isolated products have been characterized structurally and functionally for their capacity to inhibit proliferation of cultured cancer cells. Marked antitumor effects have been reported. The present review provides a detailed analysis of the natural products isolated from *C. concinna*, their antitumor properties and potential mechanism of action. Molecular targets are proposed for the lead compounds in the series.



Cryptocarya concinna Hance

Fig. 1. *Cryptocarya concinna* Hance (Lauraceae) is a tall tree largely distributed in Southeast Asia. Extracts obtained from the leaves (drawn) have revealed antioxidant properties. These extracts contain large amounts of anthocyanins which are flavonoids with a positive charge at the oxygen atom of the B-ring of basic flavonoid structure.

2. Anti-inflammatory and anti-proliferative activities of *Cryptocarya concinna* extracts

Extracts have been prepared from leaves and branches of 27 Lauraceae species and evaluated for their anti-inflammatory, antioxidant, antifungal and anti-proliferative activities. No significant effect was observed against two types of fungi, *Trametes versicolor* (white rot fungus) and *Laetiporus sulphureus* (brown-rot fungus). In contrast, most of the methanolic extracts revealed an antioxidant activity based on a radical scavenging assay with the DPPH (1,1-diphenyl-2-picrylhydrazyl) probe. The antioxidant potential of the alcoholic extract from *C. concinna* was satisfactory, neither weak nor particularly high, roughly similar to that observed with the majority of extracts tested. But interestingly, the same extract exhibited a pronounced effect in the nitric oxide (NO) inhibition assay, used to reveal the anti-inflammatory potential of the products. At the dose of 25 μg/mL, the extract reduced the production of NO in murine macrophage RAW 264.7 cells by more than 80%. Only one other species of Lauraceae (*Litsea akoensis*) produced a similarly high inhibitory effect. Moreover, the methanolic extract was found to inhibit the proliferation of human umbilical vein endothelial cells (HUVEC), with an EC_{50} of 49.4 μg/ml, but it has no effect on the proliferation of HL-60 promyelocytic leukemia cells and MCF-7 breast cancer cells (Lin et al., 2007). Clearly, the alcoholic extract of *C. concinna* leaves displays a pronounced anti-inflammatory effect and can impact cell growth. A more recent study has pointed out modest antibacterial and larvicidal activities with an essential oil made from fresh leaves of *C. concinna* subjected to hydrodistillation (Chau et al., 2020).

A methanolic extracts from the roots of the plant has been found to reduce the proliferation of the oral cancer cell lines Ca9-22 and CAL 27. The cell growth inhibitory effect was associated with induction of reactive oxygen species (ROS) in cells, mitochondrial damages (depolarization of the mitochondrial membrane potential) and cell apoptosis (Huang et al., 2014a). Later, the same authors reported that this particular root extract triggered ROS-dependent apoptosis of Ca9-22 cells and the cellular lethal effects were associated with drug-induced DNA damages and alteration of cell cycle progression (accumulation of cells in the G2/M phase). A synergistic effect was observed when these oral cells were exposed to an Ultraviolet C light in addition to the plant extract. The anti-proliferative and pro-apoptotic effects were significantly reinforced when the two active elements were combined (Chang et al., 2016a). The cellular activities have been attributed mainly to the dihydrochalcone derivative cryptocaryone (**1**) (Fig. 2) which has been isolated from *C. concinna* and from diverse *Cryptocarya* plants (Chang et al., 2016b).

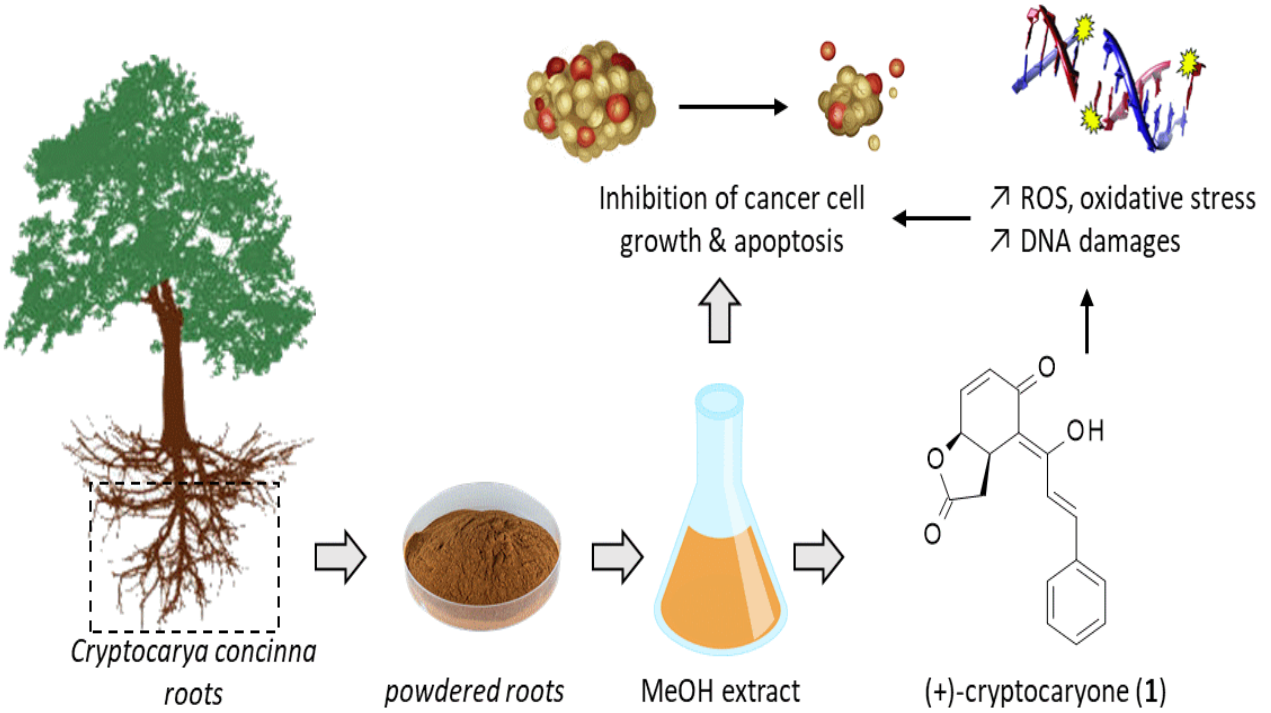


Fig. 2. Antitumor extracts have been prepared from the roots of *Cryptocarya concinna*. The extracts were found to inhibit proliferation of cultured tumor cells. The main bioactive compound isolated from those extract was the dihydrochalcone cryptocaryone (**1**) which induces a marked oxidative stress (with enhanced production of reactive oxygen species, ROS) and DNA damages in cells.

3. Anticancer natural products isolated from *Cryptocarya concinna*

3.1. Cryptoconcatones

A series of twelve α-pyrone derivatives has been isolated from the leaves and twigs of *C. concinna*. The compounds, named cryptoconcatones A-to-L (**2**-**13**), all correspond to arylalkenyl α,β-unsaturated δ-lactones, as represented in Fig. 3 (Huang et al., 2014b; Yang et al., 2016, 2017). Cryptoconcatones A-to-G (**2**-**8**) bear a central substituted alkyl chain, with a styryl ring and an α,β-unsaturated δ-lactone, at each end. They differ by the substituent on the lactone ring (R_1) or on the alkyl chain (R_2,R_3). Cryptoconcatone H (**9**) is a distinct compound with a central tetrahydropyran motif. Based on the total synthesis of the compound, the structure initially proposed has been revised. The natural product corresponds to the all-*R* stereoisomer (Della-Felice et al., 2017, 2018). Another total synthesis of cryptoconcatone H and a detailed structural analysis have confirmed that the natural product bears a *trans*- rather than *cis*-tetrahydropyran ring (Csókás and Bates, 2019). Major efforts have been deployed to define the correct structure of cryptoconcatone H (**9**). This atypical molecule is structurally close to compounds like obolactone (**14**) and cryptoyunones isolated from *C. obovata* and *C. yunnanensis*, such as cryptoyunone B (**15**) (Fig. 3) (Dumontet et al., 2004; He et al., 2020).
Cryptoconcatones I and J (**10**-**11**) belong also to a slightly distinct group because they both bear a five-membered lactone. They present the same molecular formula and differ by the position of the acetoxy group on the central alkyl chain. They are arylalkenyl α,β-unsaturated γ-lactones, for which specific synthetic approaches have been developed (Acharyya et al., 2019; Yoo et al., 2020). The synthesis of the γ-*Z*-butenolide core of cryptoconcatone I (**10**) from *E*-cinnamaldehyde requires no less than 15 steps (9.1% overall yield) (Acharyya et al., 2019). The structures of cryptoconcatone K (**12**) and its acetylated analogue cryptoconcatone L (**13**) are reminiscent to that of cryptoconcatone H (**9**) with a central tetrahydropyran motif. They bear both a hydroxyl group on the lactone ring, as for cryptoconcatones E-F-G (**6**-**8**). Unlike cryptoconcatones A-J (**2**-**11**) which were found to be inactive against cultured cancer cells, cryptoconcatones K (**12**) and L (**13**) markedly inhibited the growth in Huh7 hepatocellular carcinoma cells, with IC_{50} of 4.5 and 3.9 μM, respectively. These values are not far to that measured with the reference anticancer drug doxorubicin (IC_{50} = 1.4 μM). The two compounds were less active against U2OS human osteosarcoma cells (IC_{50} of 19.7 and 16.2 μM, respectively) (Yang et al., 2017). The marked activity against the hepatocellular carcinoma (HCC) cells warrants further investigation because HCC are aggressive tumors for which novel medication are actively needed.
Cryptoconcatones A-J (**2**-**11**) are non-cytotoxic compounds toward these cancer cells but a mild cytotoxic activity of cryptoconcatone G (**8**) has been observed at high concentrations (50 μM) when using RAW 264.7 macrophagic cells (Yang et al., 2016).

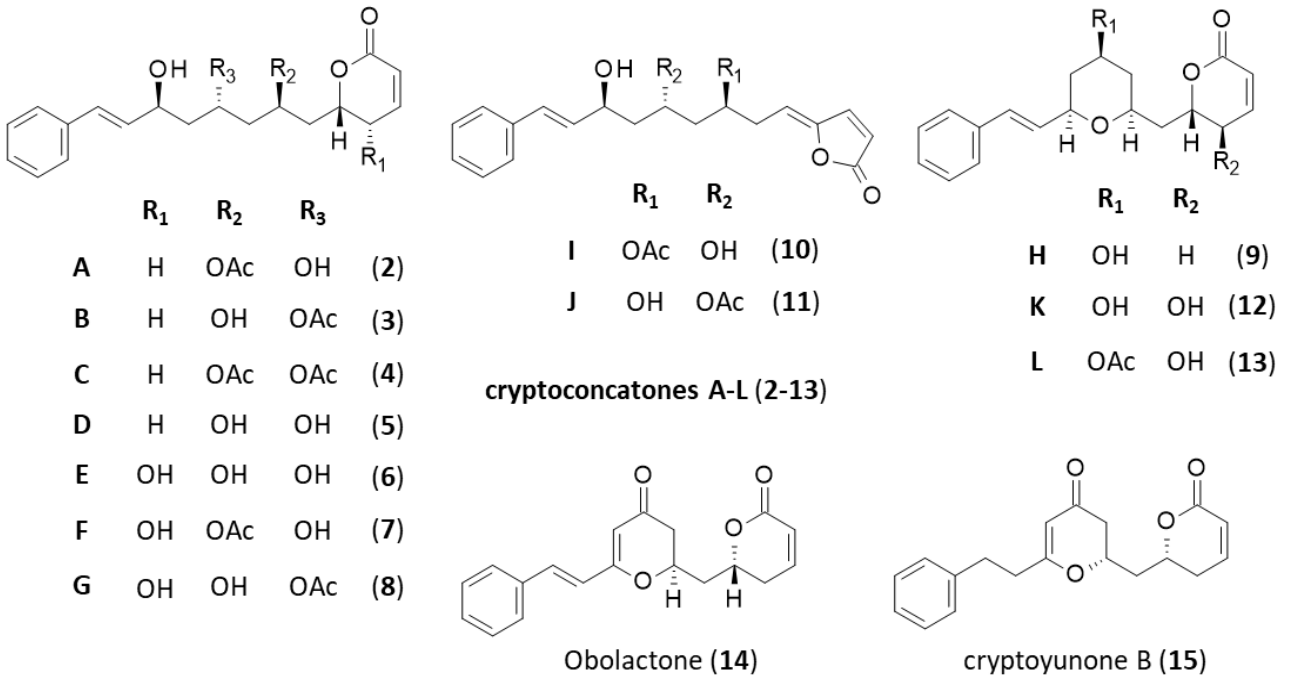


Fig. 3. Lactone derivatives. Structures of cryptoconcatones A-L (**2**-**13**) isolated from *C. concinna* and the related compounds obolactone (**14**) and cryptoyunone B (**15**).

Most of these lactone compounds display an anti-inflammatory activity, measured via the inhibition of the production of NO in lipopolysaccharide-induced RAW 264.7 macrophages. The best anti-inflammatory action was obtained with cryptoconcatones D (**5**), H (**9**) and I (**10**) (IC_{50} = 3.2, 4.2 and 3.4 μM, respectively) (Yang et al., 2016). These three compounds, lacking an acetoxy group attached to the alkenyl chain, bear an α,β-unsaturated-γ-lactone ring which is a key element for the anti-inflammatory action.

3.2. Cryptocaryone

Cryptocaryone (**1**) is a benzofurandione derivative (Fig. 2) initially isolated from the plant *Cryptocarya bourdilloni* Gamble (Lauraceae) in 1972 but an incorrect structure (dihydrochalcone) was reported at that time (Govindachari et al., 1972). The structure was revised thirteen years later, based on an X-ray analysis of the molecule (Maddry et al., 1985; Dumontet et al., 2001). These last years, the compound has been found in a variety of *Cryptocarya* species, such as *C. mackinnoniana* (Raju et al., 2022), *C. rubra* (Ren et al., 2014), *C. chinensis* (Chou et al., 2011) and *C. konishii* (Kurniadewi et al., 2010) and *C. rugulosa* (Meragelman et al., 2009). Processes have been described to obtain each enantiomer of the compound and analogues by total syntheses (Fujioka et al., 2010; Franck et al., 2010; Liu et al., 2018).

Diverse biological properties have been reported with cryptocaryone (**1**). Initially, the compound was found to inhibit the activity of the transcription factor NFκB in human lymphoma cells (Meragelman et al., 2009) and to inhibit tyrosine kinase activity *in vitro* but with a very modest potency (47% inhibition at 100 μM) (Kurniadewi et al., 2010). The molecular targets of cryptocaryone have not been identified at present. The compound displays marked cytotoxic properties against various cancer cell lines. It was found to inhibit the growth of DU145 prostate cancer cells (IC_{50} = 2.3 μM) (Hexum et al., 2012), P-388 leukemia cells (IC_{50} = 0.04 μM) (Kurniadewi et al., 2010), PC-3 prostate cancer cells (IC_{50} = 1.6 μM) (Chen et al., 2010) and HT-29 human colon cancer cells (IC_{50} = 0.32 μM) (Ren et al., 2014). Remarkably, compound (**1**) inhibits proliferation and triggers apoptosis of both androgen-independent (PC-3 and DU-145) and androgen-dependent (LNCaP) prostate cancer cells with a roughly similar potency. In PC-3 cells, the drug-induced apoptosis activation pathway included recruitment of death receptors DR4 and DR5 and their clustering and aggregation into lipid rafts, a process leading to caspases activation (Chen et al., 2010). A recent study has provided further details about the pro-apoptotic capacity of cryptocaryone (**1**) in different histotypes of prostate cancer. The drug has been found to induce a marked oxidative stress, leading to DNA damages, as judged from the increased expression of the phosphorylated histone variant γ-H2AX and increased staining of H2AX foci (Chen et al., 2022). Cryptocaryone-induced DNA damages have been observed also using HSC-3 and OC-2 oral cancer cells. Treatment of those cells for 24 hours with the compound induced expression of γ-H2AX and formation of 8-hydroxy-2′-deoxyguanosine (8-OHdG) which is an oxidative stress marker. The combination of cryptocaryone (**1**) and ultraviolet C (UVC) further enhanced those two activities leading to a larger arrest of the cell cycle in G2/M phase and a

more pronounced degree of apoptosis, with caspases activation. Cryptocaryone (**1**) exerts a radiosensitizing anti-proliferation effect on UVC irradiated oral cancer cells (Wang et al., 2022). DNA damages have been also characterized using Ca-9-22 and CAL-27 oral cancer cell lines which are both quite sensitive to cryptocaryone-induced DNA damages and oxidative stress. The extent of caspases activation, production of ROS, DNA damages and apoptosis induced by cryptocaryone in Ca-9-22 cells can be almost totally abolished in the presence of the antioxidant compound N-acetyl-cysteine, indicating clearly that it is the oxidative stress which is at the origin of the drug-induced collapse of the cells (Chang et al, 2016). The effects are not specific to oral cancer cells, as the same activities were reported using the oral and ovarian cancer cells (Chang et al, 2016; Chen et al., 2022).

Cryptocaryone (**1**) emerges as an interesting anti-inflammatory and anticancer agent, at least *in vitro* (Feng et al., 2012). An evaluation of its potency and tolerability in mice with xenografted tumors is awaited. Beyond, there is a series of cyclohexanone derivatives which should be further studied as anticancer agents, such as the related product infectocaryone isolated from *Cryptocarya* species, which have revealed interesting cytotoxic properties (Chou et al., 2010).

3.3. Cryptoconones and related flavonoids

Five flavonoids designated cryptoconones A-to-E (**16**-**20**) (Fig. 4) have been isolated from the stem wood of *C. concinna* but they were found inactive against cancer cell growth and inactive also in antibacterial and antifungal assays (Huang et al., 2014).

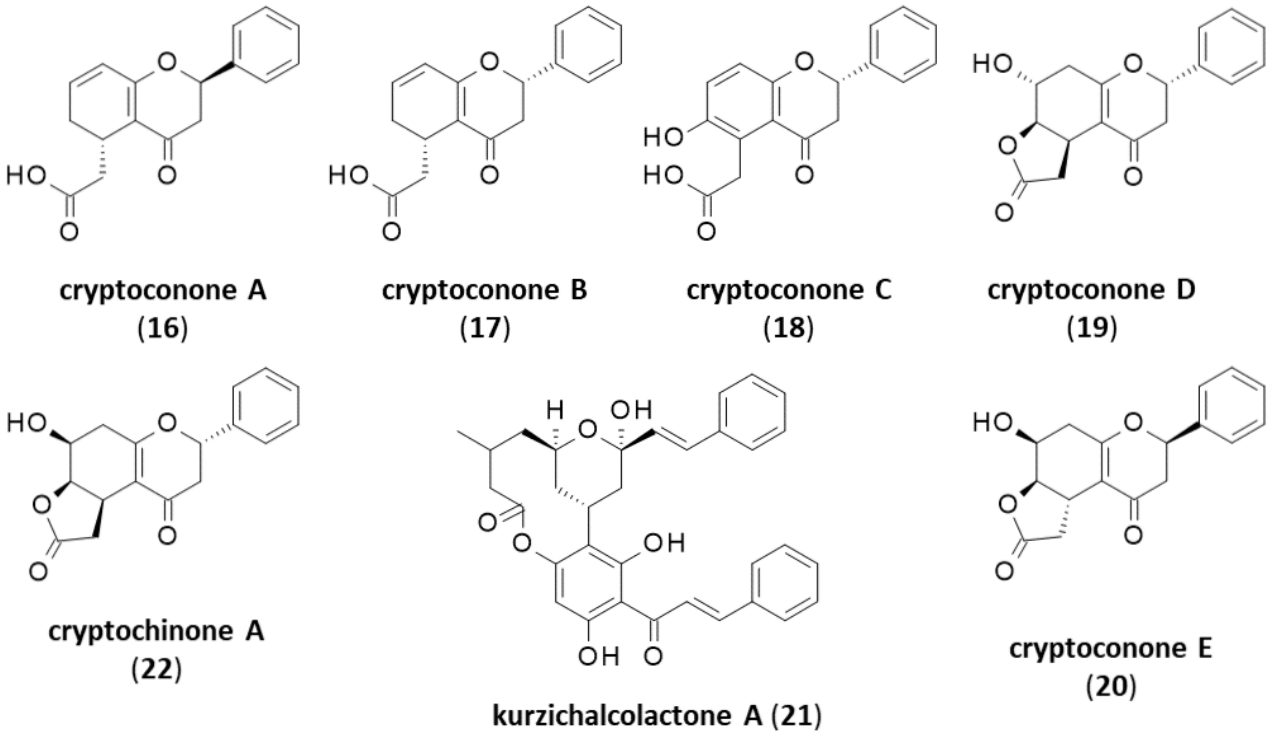


Fig. 4. Structures of cryptoconones A-E (**16**-**20**) isolated from *C. concinna* and the related flavonoids cryptochinone A (**22**). The complex flavonoid kurzichalcolactone A (**21**) has been isolated also also from *C. concinna* and other *Cryptocarya* species.

During the isolation process, the authors characterized other known flavonoids, such as kurzichalcolactone A (**21**) which can be found in other *Cryptocarya* species (Dumontet et al., 2004; Siallagan et al., 2008; Kurniadewi et al., 2010). Cryptoflavanones A-D (**16-19**) are flavanone derivatives isolated from *C. chinensis* (Chou et al., 2011). Two related compounds designated cryptoflavanones E and F have been mentioned in a meeting report (poster presentation) published in 2017, but there are no other details about these compounds isolated from *C. concinna*. This meeting report also cited a compound named concitocaryone, but without further information (Chang et al., 2017).

Another flavonoid merits mention: cryptochinone A (**22**) initially isolated from *C. Chinensis* because this compund has been found to exert an agonistic effect toward the farnesoid X receptor (FXR) (Chou et al., 2010; Lin et al., 2014). Cryptochinone A (**22**) is structurally close to cryptoconones D and E (**19**-**20**) (Fig. 4). Therefore, it would be useful to investigate the activity of cryptoconones against FXRs. FXR agonists can be useful to treat liver injuries (e.g. the potent FXR agonist

obeticholic acid FDA-approved to treat cholestatic liver disease). Recently, the targeting of the bile-regulating FXR nuclear receptors has been discussed as a novel approach to combat biliary tract cancer but also liver, colon and prostate cancers (Girisa et al., 2021; Yin et al., 2021; Sun et al., 2021).

4. Concluding remarks

Tree species of Lauraceae are abundant in eastern Asia, notably in subtropical areas. They are frequently used in folk medicine to treat infections, fevers and other diseases and symptoms. A comparison of extracts from 27 woody plants of Lauraceae grown in Taiwan has revealed that alcoholic *C. concinna* extracts are among the most potent in terms of anti-inflammatory and antiproliferative activities (Lin et al., 2007). Nutraceutical and pharmaceutical applications of *C. concinna* extracts could be envisioned. As discussed here, these extracts contain various products active against the proliferation such as cryptoconcatones. Of course, there are other of cancer cells, including flavonoids and lactones, *Cryptocarya* species of medicinal interest, notably to treat microbial infections (Zoccolotti et al., 2021). But extracts from *C. concinna* appears interesting, and perhaps insufficiently considered thus far for medicinal applications. Among the various natural products isolated from *C. concinna*, one compound in particular caught our attention: the styryl lactone cryptoconcatone D (**5**) which bears an α,β-unsaturated δ-lactone. This compound, which displays marked anti-inflammatory effects (Yang et al., 2016), presents a structural analogy with two known molecules for which the mechanism of action has been delineated, at least in part. On the one hand, a structural analogy can be seen between cryptoconcatone D (**5**) and the styryl-lactone goniothalamin (**23**) (Fig. 5) which is also a well-known anticancer agent, isolated from the medicinal plant *Goniothalamus andersonii* (Seyed et al., 2014; Pilli et al., 2019).

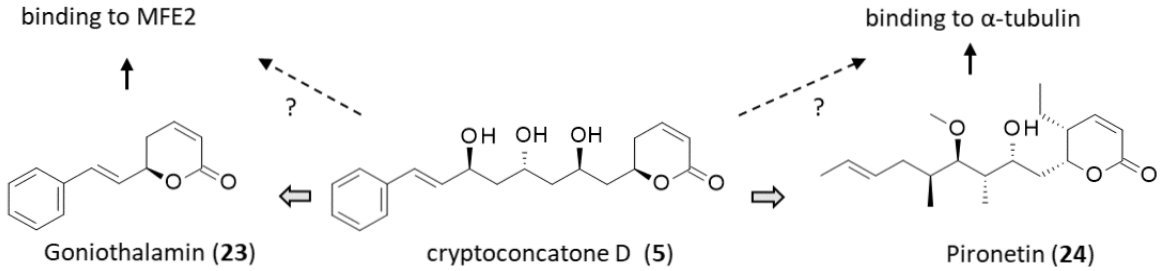


Fig. 5. The structural analogy between cryptoconcatone D (**5**) and goniothalamin (**23**) known to bind to MFE2 and pironetin (**24**) which binds to the α-tubulin.

This natural product found in diverse plants has revealed marked activity against breast cancer, inducing specific cellular lethal effects (apoptosis, necroptosis) (Khaw-On et al., 2018, 2019; Bakar et al., 2022). The drug is active *in vivo*, alone and in combination with cisplatin (Punganuru et al., 2018) and its bioavailability can be enhanced upon encapsulation into nanoparticles (Braga et al., 2020). The molecular targets of goniothalamin (**23**) remain uncertain at present but the drug has been shown to conjugate with glutathione in cells, thereby inducing a redox imbalance (Punganuru et al., 2018). Moreover, a recent analysis pointed out an interaction between goniothalamin and the peroxisomal multifunctional enzyme type2 (MFE2) which is implicated in beta-oxidation of fatty acids in peroxisomes. Upon direct binding to MFE2, goniothalamin (**23**) would be able to perturb the synthesis of lipids in cells, thereby inducing an endoplasmic reticulum stress (Sophonnithiprasert et al., 2021). By analogy, it can be hypothesized that cryptoconcatone D (**5**) can alter lipid synthesis via a MFE2-dependent mechanism.

On the other hand, cryptoconcatone D (**5**) is structurally close to the α-tubulin binder pironetin (**24**) which is a potent, but rapidly metabolized, antitumor agent (Coulup and Georg, 2019; Coulup et al., 2019). Pironetin (**24**) (Fig. 5) is known to inhibit cell division by forming a covalent adduct with a cysteine residue (Cys316) of α-tubulin (Prota et al., 2016). Therefore, it would be interesting to evaluate the tubulin-binding capacity of cryptoconcatone D (**5**). A preliminary investigation, using a computational approach (molecular docking) indicated that the interaction is highly plausible. The high-resolution crystal structure of pironetin (**24**) bound to α/β-tubulin dimer (PDB: 5FNV) can be used to investigate the interaction between cryptoconcatone D and tubulin. A model has been built, as represented in Fig. 6, and the empirical energies of interaction (ΔE) calculated. Interestingly, ΔE values of -57.3 and -60.5 kcal/mol were calculated for pironetin (**24**) and cryptoconcatone D (**5**), respectively. Therefore, the calculations suggest that cryptoconcatone D can bind equally well to the pironetin site of α-tubulin, in a position entirely compatible with the formation of a covalent bond with Cys316 (Fig. 6d). This preliminary analysis suggests that tubulin can be the molecular target of cryptoconcatone D (**5**) at the origin of the bioactivity of the product. In addition, it raises hypotheses for other natural compounds bearing a comparable α,β-unsaturated δ-lactone core. There exist a complete family

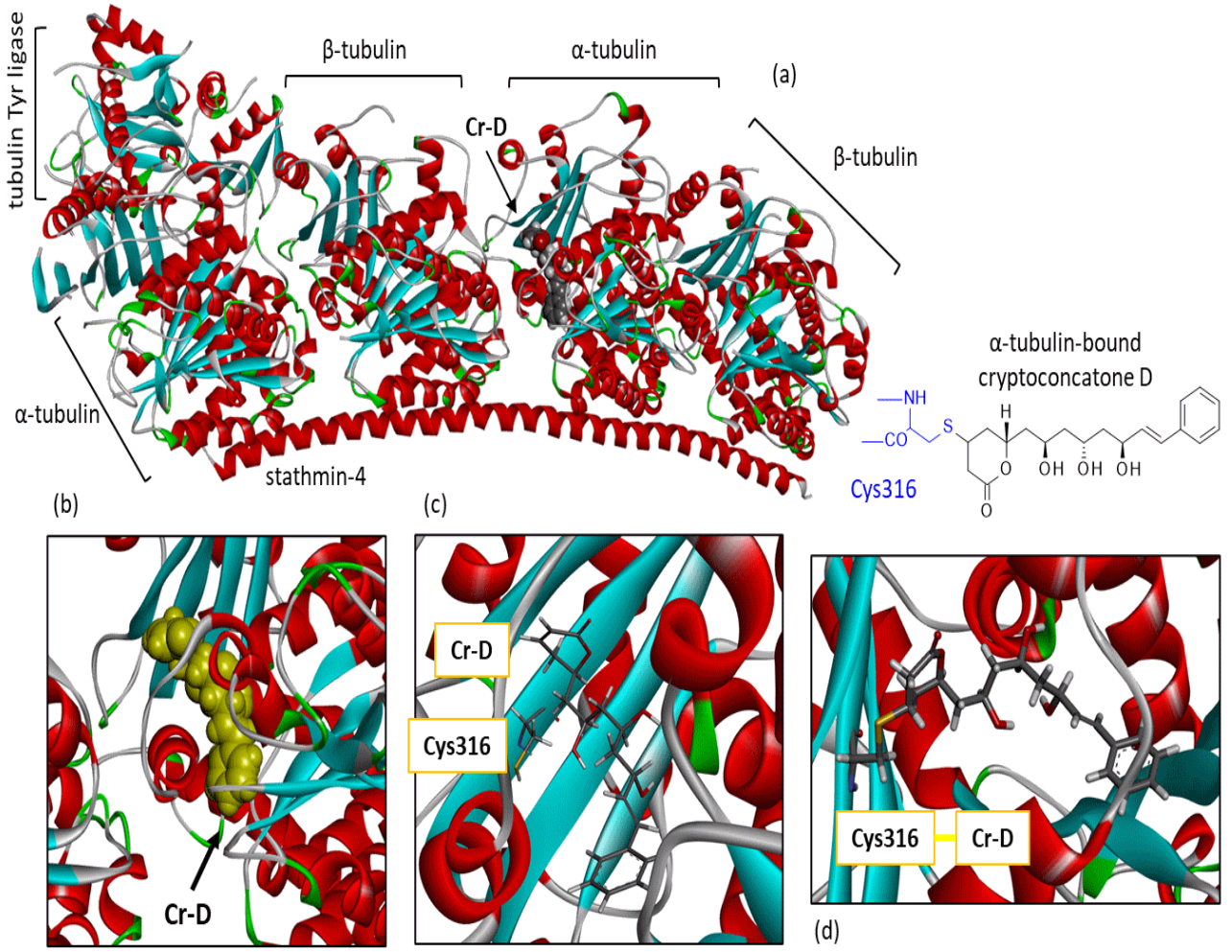


Fig. 6. Molecular model of cryptoconcatone D (Cr-D) bound to β-tubulin. (a) A docking model of Cr-D binding to the α/β-tubulin dimer interacting with stathmin-4 and tubulin tyrosine ligase (PDB access code: 5FNV) was built. Cr-D appeared to bind well to the pironetin active site of α-tubulin. (b) A close-up view of Cr-D (in yellow) bound to the active site. (c) The compound places its lactone unit in front of Cys316, at a distance amenable to covalent reaction with the thiol group of Cys316 residue. (d) A view of Cr-D bound covalently to α-tubulin via the Cys316 residue, as presented on the corresponding structure. The docking analysis was performed as described in recent studies (Bailly and Vergoten, 2021, 2022; Vergoten and Bailly, 2022).

of such lactone compounds (e.g. cryptobrachytone A-C, kurzilactones A-B, crypotocaryalactone, cryptofolione, rugulactone, cryptobrachytone, cryptolaevilactone, etc) (Boucard et al., 2007; Tsurumi et al., 2018, 2019). Natural products with a α,β-unsaturated δ-lactones are extremely diversified in plants but their mechanism of action has not been often investigated. These compounds should be tested as tubulin binders. Based on our analysis, preliminary structure-activity relationships can be deduced. In the cryptoconcatone series, the antiproliferative activity reported with cryptoconcatones K and L (**12**-**13**) suggests that the presence of central tetrahydrypyrane motif is a key element for activity. Further studies are needed to expand the SAR. To conclude, the phytochemical analysis of *Cryptocarya concinna* opens novel perspectives to better comprehend the mechanism of action of these bioactive lactone compounds.

Conflict of interest

The authors declare that there is no conflict of interest.

References

Acharyya, R.K., Pal, P., Chatterjee, S., Nanda, S., 2019. Asymmetric total synthesis of cryptoconcatone I. Org. Biomol. Chem. 17(14), 3552-3566.

Bailly, C., Vergoten, G., 2021. Interaction of obtusilactone B and related butanolide lactones with the barrier-to-autointegration factor 1 (BAF1). A computational study. Curr. Res. Pharmacol. Drug Discov. 2, 100059.

Bailly, C., Vergoten, G., 2022. Japonicone A and related dimeric sesquiterpene lactones: Molecular targets and mechanisms of anticancer activity. Inflamm. Res. 71(3), 267-276.

Bakar, S.A.A., Ali, A.M., Noor, S.N.F.M., Hamid, S.B.S., Azhar, N.A., Mohamad, N.M., Ahmad, N.H., 2022. Combination of goniothalamin and sol-gel-derived bioactive glass 45s5 enhances growth inhibitory activity *via* apoptosis induction and cell cycle arrest in breast cancer cells MCF-7. Biomed. Res. Int. 2022, 5653136.

BGO Plant Database. http://www.qsbg.org/Database/plantdb/herbarium/herbarium-specimen.asp?id=20712

Boucard, V., Broustal, G., Campagne, G.M. 2007. Synthetic approaches to α,β-unsaturated δ-lactones and lactols. Eur. J. Org. Chem. 2007, 225-236.

Braga, C.B., Kido, L.A., Lima, E.N., Lamas, C.A., Cagnon, V.H.A., Ornelas, C., Pilli, R.A., 2020. Enhancing the anticancer activity and selectivity of goniothalamin using pH-sensitive acetalated dextran (Ac-Dex) nanoparticles: A Promising platform for delivery of natural compounds. ACS Biomater. Sci. Eng. 6(5), 2929-2942.

Chang, H.S., Tang, J.Y., Yen, C.Y., Huang, H.W., Wu, C.Y., Chung, Y.A., Wang, H.R., Chen, I.S., Huang, M.Y., Chang, H.W., 2016. Antiproliferation of *Cryptocarya concinna*-derived cryptocaryone against oral cancer cells involving apoptosis, oxidative stress, and DNA damage. BMC Complement. Altern. Med. 16, 94.

Chang, H.S., Wang, C.S., Lin, C.H., Chen, I.S., Chen, Y.F., 2017. Chemical constituents and cytotoxic activities from the root of *Cryptocarya concinna*. GA, Basel, Switzerland. (https://coms.events/GA2017/data/abstracts/en/abstract_0260.html).

Chang, H.W., Tang, J.Y., Yen, C.Y., Chang, H.S., Huang, H.W., Chung, Y.A., Chen, I.S., Huang, M.Y., 2016. Synergistic anti-oral cancer effects of UVC and methanolic extracts of *Cryptocarya concinna* roots via apoptosis, oxidative stress and DNA damage. Int. J. Radiat. Biol. 92(5), 263-272.

Chau, D.T.M., Chung, N.T., Huong, L.T., Hung, N.H., Ogunwande, I.A., Dai, D.N., Setzer, W.N., 2020. Chemical compositions, mosquito larvicidal and antimicrobial activities of leaf essential oils of eleven species of Lauraceae from Vietnam. Plants (Basel) 9(5), 606.

Chen, Y.C., Kung, F.L., Tsai, I.L., Chou, T.H., Chen, I.S., Guh, J.H., 2010. Cryptocaryone, a natural dihydrochalcone, induces apoptosis in human androgen independent prostate cancer cells by death receptor clustering in lipid raft and nonraft compartments. J. Urol. 183(6), 2409-2418.

Chen, Y.C., Yang, C.W., Chan, T.F., Farooqi, A.A., Chang, H.S., Yen, C.H., Huang, M.Y., Chang, H.W., 2022. Cryptocaryone promotes ROS-dependent antiproliferation and apoptosis in ovarian cancer cells. Cells 11(4), 641.

Chou, T.H., Chen, J.J., Lee, S.J., Chiang, M.Y., Yang, C.W., Chen, I.S., 2010. Cytotoxic flavonoids from the leaves of Cryptocarya chinensis. J. Nat. Prod. 73(9), 1470-1475.

Chou, T.H., Chen, J.J., Peng, C.F., Cheng, M.J., Chen, I.S., 2011. New flavanones from the leaves of Cryptocarya chinensis and their antituberculosis activity. Chem. Biodivers. 8(11), 2015-2024.

Chudnoff, M., Tropical timbers of the world. 1984. United States Department of Agriculture, Forest Service, Agriculture Handbook Number 607.

Coulup, S.K., Georg, G.I., 2019. Revisiting microtubule targeting agents: α-Tubulin and the pironetin binding site as unexplored targets for cancer therapeutics. Bioorg. Med. Chem. Lett. 29(15), 1865-1873.

Coulup, S.K., Huang, D.S., Wong, H.L., Georg, G.I., 2019. Identification of the metabolic profile of the α-tubulin-binding natural product (-)-pironetin. J. Med. Chem. 62(3), 1684-1689.

Csókás, D., Bates, R.W., 2019. Synthesis of the proposed structure of cryptoconcatone H. Synlett 30, 178-180.

de Kok, R.P.J., 2015. A revision of Cryptocarya (Lauraceae) from Thailand and Indochina. Gardens' Bulletin Singapore 67, 309-350.

Della-Felice, F., Pilli, R.A., Sarott, A.M., 2018. Computer-guided total synthesis of natural products. Recent examples and future perspectives. J. Braz. Chem. Soc. 29(5), 1041-1075.

Della-Felice, F., Sarotti, A.M., Pilli, R.A., 2017. Catalytic asymmetric synthesis and stereochemical revision of (+)-cryptoconcatone H. J. Org. Chem. 82(17), 9191-9197.

Dumontet, V., Gaspard, C., Van Hung, N., Fahy, J., Tchertanov, L., Sévenet, T., Guéritte, F., 2001. New cytotoxic flavonoids from *Cryptocarya infectoria*. Tetrahedron 57(29), 6189-6196.

Dumontet, V., Van Hung, N., Adeline, M.T., Riche, C., Chiaroni, A., Sévenet, T., Guéritte, F., 2004. Cytotoxic flavonoids and alpha-pyrones from *Cryptocarya obovata*. J. Nat. Prod. 67(5), 858-862.

Feng, R., Guo, Z.K., Yan, C.M., Li, E.G., Tan, R.X., Ge, H.M., 2012. Anti-inflammatory flavonoids from *Cryptocarya chingii*. Phytochemistry 76, 98-105.

Franck, G., Brödner, K., Helmchen, G., 2010. Enantioselective modular synthesis of cyclohexenones: Total syntheses of (+)-crypto- and (+)-infectocaryone. Org. Lett. 12(17), 3886-3889.

Fujioka, H., Nakahara, K., Oki, T., Hirano, K., Hayashi, T., Kita, Y., 2010. The first asymmetric total syntheses of both enantiomers of cryptocaryone. Tetrahedron Lett. 51(15), 1945-1946.

Girisa, S., Henamayee, S., Parama, D., Rana, V., Dutta, U., Kunnumakkara, A.B., 2021. Targeting farnesoid X receptor (FXR) for developing novel therapeutics against cancer. Mol. Biomed. 2(1), 21.

Govindachari, T.R., Parthasarathy, P.C., 1972. Cryptocaryone, a novel 5',6'-dihydrochalcone, from *Cryptocarya bourdilloni* gamb. Tetrahedron Lett. 33, 3419-3420.

He, Q., Fan, Y., Liu, Y., You, Y.X., Rao, L., Su, Y., Xu, Y.K., Lin, B., Zhang, C.R., 2022. Cytotoxic α-pyrone derivatives from *Cryptocarya yunnanensis*. Nat. Prod. Res. 36(4), 918-924.

Hexum, J.K., Tello-Aburto, R., Struntz, N.B., Harned, A.M., Harki, D.A., 2012. Bicyclic cyclohexenones as inhibitors of NF-κB signaling. ACS Med. Chem. Lett. 3(6), 459-464.

Huang, H.W., Chung, Y.A., Chang, H.S., Tang, J.Y., Chen, I.S., Chang, H.W., 2014a. Antiproliferative effects of methanolic extracts of *Cryptocarya concinna* Hance roots on oral cancer Ca9-22 and CAL 27 cell lines involving apoptosis, ROS induction, and mitochondrial depolarization. Sci. World J. 2014, 180462.

Huang, W., Zhang, W.J., Cheng, Y.Q., Jiang, R., Wei, W., Chen, C.J., Wang, G., Jiao, R.H., Tan, R.X., Ge, H.M., 2014b. Cytotoxic and antimicrobial flavonoids from *Cryptocarya concinna*. Planta Med. 80(11), 925-930.

Khaw-On, P., Pompimon, W., Banjerdpongchai, R., 2018. Apoptosis induction via ATM phosphorylation, cell cycle arrest, and er stress by goniothalamin and chemodrugs combined effects on breast cancer-derived MDA-MB-231 Cells. Biomed. Res. Int. 2018, 7049053.

Khaw-On, P., Pompimon, W., Banjerdpongchai, R., 2019. Goniothalamin induces necroptosis and anoikis in human invasive breast cancer MDA-MB-231 Cells. Int. J. Mol. Sci. 20(16), 3953.

Kurniadewi, F., Juliawaty, L.D., Syah, Y.M., Achmad, S.A., Hakim, E.H., Koyama, K., Kinoshita, K., Takahashi, K., 2010. Phenolic compounds from *Cryptocarya konishii*: Their cytotoxic and tyrosine kinase inhibitory properties. J. Nat. Med. 64(2), 121-125.

Lin, C.T., Chu, F.H., Tseng, Y.H., Tsai, J.B., Chang, S.T., Wang, S.Y., 2007. Bioactivity investigation of Lauraceae trees grown in Taiwan. Pharm. Biol. 45(8), 638-644.

Lin, H.R., Chou, T.H., Huang, D.W., Chen, I.S., 2014. Cryptochinones from *Cryptocarya chinensis* act as farnesoid X receptor agonists. Bioorg. Med. Chem. Lett. 24(17), 4181-4186.

Liu, J., Zhou, G., Zhang, D., 2007b. Effects of acidic solutions on element dynamics in the monsoon evergreen broad-leaved forest at Dinghushan, China. Part 2: dynamics of Fe, Cu, Mn and Al. Environ. Sci. Pollut. Res. Int. 14(3), 215-218.

Liu, J., Zhou, G., Zhang, D., 2007a. Simulated effects of acidic solutions on element dynamics in monsoon evergreen broad-leaved forest at Dinghushan, China. Part 1: dynamics of K, Na, Ca, Mg and P. Environ. Sci. Pollut. Res. Int. 14(2), 123-129.

Liu, X., Jia, J., Jia, Y., Gu, H., Luo, J., Chen, X., 2018. A Flexible and divergent strategy to flavonoids with a chiral A-ring featuring intramolecular michael addition: Stereoselective synthesis of (+)-cryptocaryone, (+)-cryptogione f, and (+)-cryptocaryanones A and B, as well as (+)-cryptochinones A and C. Org. Lett. 20(7), 1945-1948.

Maddryv, J.A., Joshi, B.S., Newton, M.G., Pelletier, S.W., Partasarathy, P.C., 1985. Crytocaryone: A revised structure. Tetrahedron Lett. 26(45), 5491-5492.

Meragelman, T.L., Scudiero, D.A., Davis, R.E., Staudt, L.M., McCloud, T.G., Cardellina, J.H., 2nd, Shoemaker, R.H. 2009. Inhibitors of the NF-kappaB activation pathway from *Cryptocarya rugulosa*. J. Nat. Prod. 72(3), 336-339.

Pilli, R.A., de Toledo, I., Meirelles, M.A., Grigolo, T.A., 2019. Goniothalamin-related styryl lactones: Isolation, synthesis, biological activity and mode of action. Curr. Med. Chem. 26(41), 7372-7451.

Prota, A.E., Setter, J., Waight, A.B., Bargsten, K., Murga, J., Diaz, J.F., Steinmetz, M.O., 2016. Pironetin binds covalently to αCys316 and perturbs a major loop and helix of α-tubulin to inhibit microtubule formation. J. Mol. Biol. 428(15), 2981-2988.

Punganuru, S.R., Madala, H.R., Arutla, V., Srivenugopal, K.S., 2018. Selective killing of human breast cancer cells by the styryl lactone (R)-goniothalamin is mediated by glutathione conjugation, induction of oxidative stress and marked reactivation of the R175H mutant p53 protein. Carcinogenesis 39(11), 1399-1410.

Raju, R., Gunawardena, D., Reddell, P., Münch, G., 2022. Cryptocaryoic acids A - C: New phenyl alkyl acids isolated from the leaves of Australian rainforest plant *Cryptocarya mackinnoniana*. Fitoterapia 162, 105266.

Ren, Y., Yuan, C., Qian, Y., Chai, H.B., Chen, X., Goetz, M., Kinghorn, A.D., 2014. Constituents of an extract of *Cryptocarya rubra* housed in a repository with cytotoxic and glucose transport inhibitory effects. J. Nat. Prod. 77(3), 550-556.

Seyed, M.A., Jantan, I., Bukhari, S.N., 2014. Emerging anticancer potentials of goniothalamin and its molecular mechanisms. Biomed. Res. Int. 2014, 536508.

Siallagan, J., Hakim, E.H., Syah, Y.M., Juliawaty, L.D., Achmad, S.A., Makmur, L., Mujahidin, D., 2008. Secondary metabolites kurzichalcolactone A and B from *Cryptocarya lucida* Blume (Lauraceae). Proceeding of The International Seminar on Chemistry, pp. 225-228.

Sophonnithiprasert, T., Aruksakunwong, O., Tashiro, E., Kondoh, Y., Muroi, M., Osada, H., Imoto, M., Watanapokasin, R., 2020. Interaction between goniothalamin and peroxisomal multifunctional enzyme type 2 triggering endoplasmic reticulum stress. Heliyon 6(10), e05200. Corrigendum in Heliyon 2021, 7(2), e05907.

Sun, L., Cai, J., Gonzalez, F.J., 2021. The role of farnesoid X receptor in metabolic diseases, and gastrointestinal and liver cancer. Nat. Rev. Gastroenterol. Hepatol. 18(5), 335-347.

Tsurumi, F., Miura, Y., Nakano, M., Saito, Y., Fukuyoshi, S., Miyake, K., Newman, D.J., O'Keefe, B.R., Lee, K.H., Nakagawa-Goto, K., 2019. Spiro[3.5]nonenyl meroterpenoid lactones, cryptolaevilactones G-L, an ionone derivative, and total synthesis of cryptolaevilactone M from *Cryptocarya laevigata*. J. Nat. Prod. 82(9), 2368-2378.

Tsurumi, F., Miura, Y., Saito, Y., Miyake, K., Fujie, T., Newman, D.J., O'Keefe, B.R., Lee, K.H., Nakagawa-Goto, K., 2018. Secondary metabolites, monoterpene-polyketides containing a Spiro[3.5]nonane from *Cryptocarya laevigata*. Org. Lett. 20(8), 2282-2286.

Vergoten, G., Bailly, C., 2022. Molecular docking study of GSK-3β interaction with nomilin, kihadanin B, and related limonoids and triterpenes with a furyl-δ-lactone core. J. Biochem. Mol. Toxicol. 36(9), e23130.

Wang, S.C., Chang, H.S., Tang, J.Y., Farooqi, A.A., Kuo, Y.T., Hsuuw, Y.D., Lee, J.W., Chang, H.W., 2022. Combined treatment with cryptocaryone and ultraviolet C promotes antiproliferation and apoptosis of oral cancer cells. Int. J. Mol. Sci. 23(6), 2981.

Wu, M., Wei, C.R., Liao, J.Z., Zhong, L.X., Huang, S.D., Qin, W.M., 2020. Growth law and stand regeneration characteristics of *Cryptocarya concinna* plantation. J. Southern Agricult. 51(9), 2199-2204.

Yang, B.Y., Kong, L.Y., Wang, X.B., Zhang, Y.M., Li, R.J., Yang, M.H., Luo, J.G., 2016. Nitric oxide inhibitory activity and absolute configurations of arylalkenyl α,β-unsaturated δ/γ-lactones from *Cryptocarya concinna*. J. Nat. Prod. 79(1), 196-203.

Yang, B.Y., Shi, Y.M., Luo, J.G., Kong, L.Y., 2017. Two new arylalkenyl α,β-unsaturated δ-lactones with cytotoxic activity from the leaves and twigs of *Cryptocarya concinna*. Nat. Prod. Res. 31(12), 1409-1413.

Yin, Y., Wang, M., Gu, W., Chen, L., 2021. Intestine-specific FXR agonists as potential therapeutic agents for colorectal cancer. Biochem. Pharmacol. 186, 114430.

Yoo, W.J., Chen, W., Nguyen, T.V.Q., Kobayashi, S., 2020. One-Pot synthesis of α,β-unsaturated γ-lactones and lactams via a sequential *trans*-hydroalumination and catalytic carboxylation of propargyl alcohols and amines with carbon dioxide. Org. Lett. 22(6), 2328-2332.

Yu, Z., Zhang, P., Lin, W., Zheng, X., Cai, M., Peng, C., 2019. Sequencing of anthocyanin synthesis-related enzyme genes and screening of reference genes in leaves of four dominant subtropical forest tree species. Gene 716, 144024.

Zhang, M., Yahara, T., Tagane, S., Rueangruea, S., Suddee, S., Moritsuka, E., Suyama, Y., 2020. *Cryptocarya kaengkrachanensis*, a new species of Lauraceae from Kaeng Krachan National Park, southwest Thailand. PhytoKeys 140, 139-157.

Zhang, T.J., Zheng, J., Yu, Z.C., Huang, X.D., Zhang, Q.L., Tian, X.S., Peng, C.L., 2018. Functional characteristics of phenolic compounds accumulated in young leaves of two subtropical forest tree species of different successional stages. Tree Physiol. 38(10), 1486-1501.

Zhu, H., Zhang, T.J., Zhang, P., Peng, C.L., 2016. Pigment patterns and photoprotection of anthocyanins in the young leaves of four dominant subtropical forest tree species in two successional stages under contrasting light conditions. Tree Physiol. 36(9), 1092-104.

Zoccolotti, J.O., Cavalheiro, A.J., Tasso, C.O., Ribas, B.R., Ferrisse, T.M., Jorge, J.H., 2021. Antimicrobial efficacy and biocompatibility of extracts from *Cryptocarya* species. PLoS One 16(12), e0261884.