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Research

An *in silico* Approach For Identification of Potential Therapeutic Targets For Cancer Treatment From *Celastrus hindsii* Benth

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ABSTRAK

Celastrus hindsii Benth., a medicinal plant celebrated for its traditionally medicinal and practically therapeutic properties, has been used for generations in Vietnam to support the treatment of ulcers, tumors, and inflammation. The difference between several phenotypes, primarily identified as Broad Leaf (BL) and Narrow Leaf (NL), has been clarified by convincing scientific evidence through our previous proteomics study, which also revealed several bioactive proteins and peptides. Therefore, based on the findings, this study further investigated their therapeutic properties using a bioinformatics tool (BLASTP) and analyzing literature data. The results showed the distinguished variations in protein profile between the NL and BL proteomes and revealed five significant proteins with therapeutic properties. Of these, three proteins can have anti-tumor and anti-inflammatory activity and have been proven effective in cancer treatment. Therefore, *C. hindsii*, particularly the BL phenotype with elevated levels of therapeutic proteins, could be a promising plant candidate for future intensive research and applications for cancer treatment.

Key words: Bioinformatics, *Celastrus hindsii*, *in silico* approach, medicinal plant, therapeutic targets

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INTRODUCTION

Medicinal plants are among the major and important groups of crops that provide a rich source of new vitamins and highly diverse specialized proteins with critical pharmacological properties. These plants have been used in various traditional medicinal practices to prevent and treat disease for a long time in Southern China, Northern Vietnam, Malaysia, and Myanmar (Chen *et al*., 2016). In modern medicine, specialized plant proteins have been utilized in therapeutic applications and synthesizing new bioactive compounds, which are associated with protective roles on human health due to their anti-inflammatory effect (Pham *et al*. 2022), anti-tumor activity (Taniya *et al*., 2020), antithrombotic effects (Lafarga *et al*., 2020), antimicrobial feature (Zhou *et al*., 2020) and antioxidant activities (Tonolo *et al*., 2020) and related to a reduction in the risk of cancer, cardiovascular, and other chronic diseases (Cijo *et al*., 2017). Plant-derived proteins have been becoming attractive as animal counterparts found challenges to meet the global population's demand. Technically, these bioactive compounds are emerging as their eco-friendly sustainability for producing protein hydrolysates or bioactive peptides. After being released into the bloodstream and processed by the intestine, their bioavailability will have a physiological influence on the specific sites.

Celastrus hindsii Benth. has been extensively cultivated and exploited over the last decades in Vietnam, especially for supporting the treatment of several chronic diseases, including ulcers, tumors, and inflammation. Recently, some phytochemical studies have revealed that *C. hindsii* possesses various phytochemicals (Hu *et al*., 2014; Kuo *et al*., 1995). Ly *et al*., (2006) investigated this medicinal

plant bioactivity and reported that antioxidant compounds such as vitamins and phenolic compounds were also purified from *C. hindsii* leaves. It is believed that *C. hindsii* possesses promising bioactive compound candidates, particularly its specialized metabolites. Therefore, the medicinal plant *C. hindsii* has been attracting more and more attention internationally, not only because of its traditional reputation but also its potential for contemporary medicine.

Our previous phytochemical and proteomic research on *C. hindsii* used plant samples collected from various locations (Nguyen *et al*., 2020a; Nguyen *et al*., 2020b). Metabolite investigations in the previous study showed significant differences in the quantity and activity of vitamin E, flavonoids, phospholipids, proline, and glutathione between narrow-leaf (NL) and broad-leaf (BL) varieties. Therefore, the results have provided useful information to select an appropriate variety for conservation and crop improvement. Also, the proteomic investigation showed that protein content in BL was also measured significantly higher than that in NL, and their biological functions varied from facilitating growth and development to being involved in secondary metabolite biosynthesis and post-translational modification. The proteomics study used Mascot to identify the peptides, which were then further confirmed by data mining using the NCBI database to determine similarity with known proteins.

To date, studies researching the medicinal plant *C. hindsii* to clarify the therapeutic properties of these proteins are limited. Therefore, such research could help gain a new understanding of the therapeutic properties of *C. hindsii*. The current study, for the very first time to the best of our knowledge, investigates further insight into *C. hindsii* therapeutic availability.

MATERIALS AND METHODS

Study area

This subsequent research expansion was a part of the project conducted from 12/2017 to 06/2019 in the Life Science laboratory, Faculty of Science, University of Technology Sydney, Australia. The scope of the previous study was to clarify the molecular mechanism causing morphological and biochemical differentiation among phenotypes of *C. hindsii* using proteomics techniques. The promising results revealed some proteins and peptides that might potentially possess therapeutic properties however they were not discussed regarding their therapeutic importance. Therefore, the follow-up bioinformatics research activity on these potential bioactive proteins has been implemented to investigate their therapeutic functions thoroughly. The activity was carried out at the Center for Medicinal Materials laboratory, Hung Vuong University, Vietnam, from 7/2019 to the present.

Bioinformatics

The previous study described the protein variation between NL and BL using 2D-PAGE coupled with MS (Nguyen *et al*., 2020a). Protein spots were identified as up-regulated or down-regulated when there was a change in volume variation (1.5-fold, $p<0.05$) (De Filippis & Magel, 2012). The identity of proteins and peptides was revealed thanks to MS and PEAKS Studio software. In this study, potential therapeutic protein and peptide sequences underwent further search in the NCBI database and protein BLAST (based on the E-value generated and % similarity). A minimal significance of 1e-3 and an identity percentage (>75%) were set as the threshold. The GO database, BLAST annotations, and information published in the literature. As the peptides were identified, their therapeutic functions were scoured in the NCBI database and Google Scholar platform. The roles of these peptides described in other medicinal plant species were also discussed to clarify their functions in plants.

RESULTS AND DISCUSSION

Differential therapeutic proteins

By data mining method and searching published papers, several proteins identified were revealed in detail with therapeutic properties. Their abundance was compared between NL and BL phenotypes by visualizing in the 2D gels (Figure 1).

The protein distribution shows a significant difference in the two phenotypes of *C. hindsii*. A total of 12 protein spots could have possible identifications (Nguyen *et al*., 2020a). Four proteins (number 5, 8, 9, 10) were discussed thoroughly in the literature regarding their therapeutic importance (Table 1).

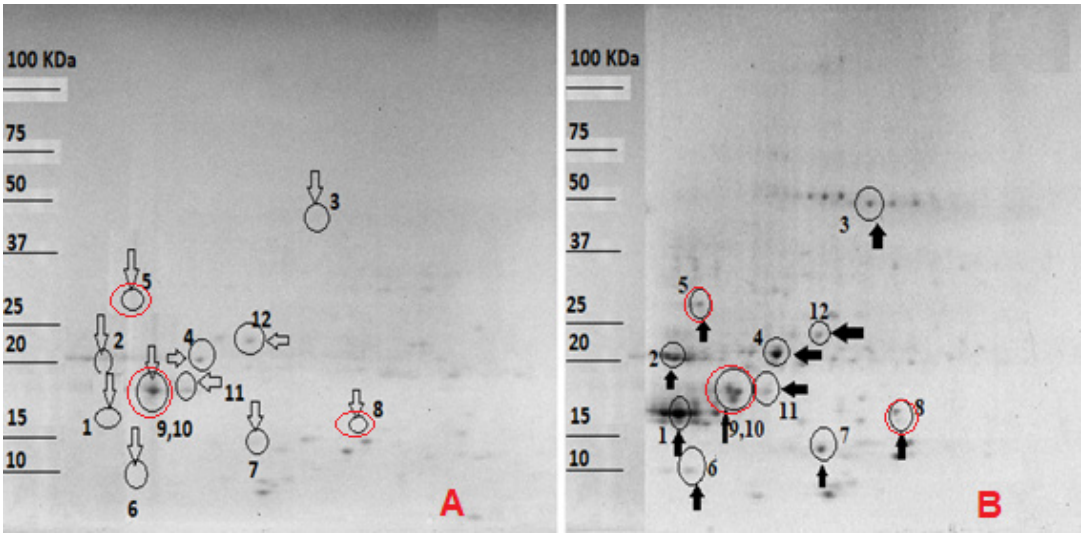

Fig. 1. Distribution of therapeutic proteins expressed in NL (A) and BL (B).
(Upper pointed arrow: up-regulated; down-pointed arrow: down-regulated; red circle: therapeutic proteins)

Table 1. Differentially expressed proteins between NL and BL related to therapeutic property

Spot No.	Mascot score	Protein name	Regulation	BLAST Score	E-value	Identity
High score						
9	96	Kunitz trypsin protease inhibitor	Upregulation	389	7e-137	100%
10	55	Cullin-4	Upregulation	1509	0.0	100%
Low score						
5	15	β-1,3-galactosyltransferase 14	Upregulation	54.5	2e-07	100%
	24	Endoribonuclease Dicer homolog	Upregulation	49.4	5e-06	100%
8	22	Staphylococcal nuclease domain-containing protein 1	Upregulation	50.3	4e-06	100%

Potential for new bioactive compounds

By comparative proteomic analysis, the current study found some proteins and peptides that play a critical role in 'state–of–the–art' advanced therapeutic intervention in human diseases. However, not all protein spots were confidentially identified by Mascot scores, and further searches for homologies were performed by UniProt (MultiIdent tool) and the NBCI (BLAST tool). This uncertainty was probably because of the unavailability of protein information in the current databases and poorly generated MS/MS data. Therefore, two categories (high scores & low scores) of identified proteins based on their matchings against selected databases were identified and detailed in Table 2. For both groups, we found proteins correlated with medicinal properties. Therefore, it is worth briefly discussing their importance and implications associated with the modern development of pharmaceuticals and human disease therapies. Interestingly, most of these gene products and proteins have been up-regulated in BL of *C. hindsii*, indicating that this phenotype is probably a superior cultivar for the development of medicinal plant crop systems.

Proteins with anti-tumor/anti-inflammatory activity and therapeutic applications
Kunitz-trypsin type proteinase inhibitor (high score proteins)

Kunitz-trypsin type proteinase inhibitor (KTI) has been well-known for its defensive role in protecting plant tissues from cell damage caused by biotic stresses. Although these plant-derived protease inhibitors have limited practical commercial use, recent studies have revealed more pharmaceutical properties (Roy *et al*., 2018). KTI shows high proficiency against invasive tumor growth and metastasis of brutal human cancers (Cid-Gallegos *et al*., 2022). Since KTIs are unlikely susceptible to different temperatures and abundant in *C. hindsii*, it is claimed that KTIs might be associated with anti-tumor and anti-inflammatory properties.

Dicer and its biogenesis product – mi/siRNAs (both low-scored proteins)

Dicer is a vital component of the RNAi and is stably conserved in organisms, especially plants. Interestingly, many organisms encode multiple Dicer members, and in distinct organisms, multiple Dicers are involved in the RNAi pathway (Fukudome & Fukuhara, 2017). Dicer showed upregulation in BL of *C. hindsii*, suggesting its role in the growth and development of this phenotype. It is likely linked to the biosynthetic activity of sRNAs. Other studies also revealed that miRNAs are involved in various metabolic processes such as the essential oil regulation pathway in *Mentha spp*, biosynthesis of gingerol in *Zingiber officinale* (Singh *et al*., 2016), and the phytochemical biosynthesis in *Curcuma longa* (Singh & Sharma, 2017). Therefore, the elevated level of Dicer could be associated with BL's superior growth and probably attributed to the therapeutic properties of this species.

Considered a contemporary therapeutic target in clinical studies, the abundance of plant miRNA has been demonstrated to be successful in mammalian disease therapies, especially in cancer treatment. Several initial demonstrations of the cross-kingdom miRNA-regulated phenomenon were recorded by Chin *et al*. (2016), indicating that mammalians can acquire miRNAs through food intake and can function on target genes to suppress the growth of tumors. As a result, the hypothesis was drawn that mammalian tumor suppressor miRNAs produced by engineered edible plants may be an effective, nontoxic, and inexpensive chemo-preventive treatment for human cancers (Iravani & Varma 2019). In humans, it was estimated that most protein-coding genes are targeted by miRNAs, influencing physiological processes. Therefore, a diverse array of human diseases is related to the dysregulation of miRNAs, particularly tumor suppressor miRNAs (Mohammadi *et al*., 2017; Nabih, 2020).

Recent studies have addressed this controversy and confirmed that ingested miRNAs and small non-coding RNAs from plant sources taken up by the digestive system were delivered to the recipient cells, including Tudor staphylococcal nuclease proteins (Otsuka *et al*., 2018). Such studies have further confirmed the potential of bioengineering medicinal plants, including *C. hindsii*, to produce therapeutic miRNAs (Witwer & Hirschi, 2014).

β-*1,3-galactosyltransferase and its biosynthetic product, arabinogalactan-proteins (both low-scored proteins)*

Plant cell wall proteoglycans (AGPs) are composed primarily of galactose and arabinose linked to proteins rich in hydroxyproline, serine, and threonine (Ndeh & Gilbert, 2018). AGPs isolated from *Larix occidentalis*, *Panax ginseng*, *and Coffea arabica* were capable of activating macrophages *in vitro* by augmenting nitric oxide, superoxide anion, and cytokine production (Nosáľová *et al*., 2011). The purified AGPs from the *Endopleura uchi* bark exhibited an anti-proliferative effect against HeLa cells (Bento *et al*., 2014) and blocked metastasis of liver tumor cells. An AGP from alkaline extracts of green and black teas was described and presented a significant gastro-protective action (Scoparo *et al*., 2016). Interestingly, AGPs from baobab and acacia seeds could modulate skin innate immune responses conferred by immunological and dermatological activities (Zahid *et al*., 2017). Several crude plant glycoproteins have been proven to be anti-inflammatory and anti-cancerous in mammalians via oral administration (Rozov *et al*., 2018). The possibility of developing medicinal crops for bioactive compound extractions from raw materials (leaves, stems, roots) has become promising in attempting to produce precious health benefits, and it may also be true in the case of the medicinal plant *C. hindsii*.

Recently, it has been evident that a lack of carbohydrate attachment to proteins has been implicated in some human diseases. The congenital disorders of glycosylation represent a group of systemic diseases characterized most prominently by neurological and developmental deficiencies, which have been well described at a molecular level (Nakanishi & Yoshikawa, 2016). Taken together, β-1,3-galactosyltransferase and its biosynthetic products, arabinogalactan-proteins, should be further studied to extend our understanding of their therapeutic properties.

Proteins overexpressed in tumor cells and their therapeutic applications

Cullin-4 associated E3 ligase (high score protein)

In *C. hindsii*, Cullin-4 proteins were found up-regulated in BL. This type of protein is the central part of the CRL system and is up-regulated in BL. The finding suggested that protein degradation extensively occurred, probably due to the ubiquitin-proteasome system. That mechanism would be the plant's response to various biotic stresses. Clinically, the correlation between cullin-4-associated E3 ligases and several types of cancers is strongly related. E3 ligases can also recognize various substrates to participate in various cellular processes, such as DNA damage and repair, cell death, and cell cycle progression (Kerzendorfer *et al*., 2011).

Table 2. Summary of proteins with pharmaceutical and human therapeutic implications

Protein No.	Protein/ Biochemical role	Human health effects/ References
	Proteins with anti-tumor/anti-inflammatory activity and therapeutic applications	
9	Kunitz - trypsin type proteinase inhibitor Defensive role against biotic stresses	- Inhibits trypsin-like enzymes and has some fungicidal activity. - Prevents the proliferation of colorectal adenocarcinoma and B16F1 melanoma cells. (Cid-Gallegos *et al*., 2022)
8	Dicer Catalyzes the biosynthesis of mi/siRNAs	- Associates with prominent and important types of cancers like breast cancer, leukemia, and lung cancer (Chin *et al*., 2016). - Deregulates miRNAs and acts on invasion and metastasis in epithelial to mesenchymal transition (EMT) of cancer cells (Mohammadi *et al*., 2017; Nabih, 2020).
5	β-1,3-galactosyl-transferase Catalyzes the biosynthesis of arabinogalactan-proteins	- Exhibits anti-proliferative effect on HeLa cells; blocks metastasis of liver tumor cells; induces apoptosis in breast cancer cells (Bento *et al*., 2014). - Presents an improvement in gastro-protective action (Scoparo *et al*., 2016). - Modulates the skin's innate immune system (Zahid *et al*., 2017).
	Proteins overexpressed in tumor cells and their therapeutic applications	
10	Cullin-4 Controls cell cycle, DNA damage, DNA repair and apoptosis	Associates with reducing tumor size, and affects cell proliferation, migration, invasion, and cancer aggressiveness. (Cheng *et al*., 2019).
8	Staphylococcal nuclease domain-containing protein Transcriptional regulator via mRNA splicing and stability	- Contributes to cell proliferation, colony, and tumor formation (Li *et al*., 2018). - High expression in invasive/metastatic breast cancer cell lines compared to poor cancer lines (Zhu & Tan, 2017; Xing *et al*., 2018).

The ubiquitin-proteasome system promotes the timely degradation of short-lived proteins with critical regulatory roles in many biological processes (Cui *et al*., 2016). Cullin-RING ubiquitin ligase 4 (CRL4) controls the cell cycle, DNA damage repair, and apoptosis. CRL4 proteins, including Cullin4A and Cullin4B, often accumulate in human malignancies. Overexpression of Cullin4A/B has been found in many cancers and is generally associated with tumor size, cell proliferation, migration, invasion, and cancer aggressiveness (Jang *et al*., 2018). The elevated CRL4 attenuated DNA damage repair and increased genome instability is believed to facilitate tumorigenesis. Combined, Cullin4 can influence human disease development thanks to regulating cellular processes associated with reducing tumor size and affects cell proliferation, migration, invasion, and cancer aggressiveness (Cheng *et al*. 2019). Therefore, Cullin4 can provide new insights into cancer diagnosis and treatment, especially identifying CRL substrates, which is little known.

Staphylococcal nuclease domain-containing protein (low score protein) – biomarker in cancer prognostic

Staphylococcal nuclease domain-containing protein (TSN) is conserved in all studies organisms (Li *et al*., 2018) and plays as a component of RNA-induced silencing complexes (RISCs). It has been researched thoroughly as a significant mediator of metastasis. In plant systems, the molecular function of TSN has not been described thoroughly, most have been characterized in the model plant *Arabidopsis* as a transcriptional regulator and a mRNA splicing and stability factor in response to stresses (Yan *et al*., 2014). This is probably the first time in the literature that TSN has been reported to be accumulated in a medicinal plant like *C. hindsii,* and it might protect the plant from stress-induced cell death. In contrast to plant systems, TSN has been researched thoroughly in mammalian systems, particularly in

humans, as it has crucial roles in cancer (Li *et al*., 2018). TSN is a nuclease in RISCs and is required for optimum RISC activities in facilitating small interfering RNA (siRNA) and micro RNA (miRNA) mediated silencing of some reporter genes (Yu *et al*., 2017). It has become evident that its increased expression is closely associated with various cancers, indicating that TSN is an attractive agent for anti-cancer therapeutic applications and a potent tumor marker. This is probably due to its role in stimulating transcription, mRNA splicing, and silencing. Other studies indicated that TSN would be acceptable for novel diagnostics and prognoses of colorectal cancer (Zhu & Tan, 2017) and lung cancer (Xing *et al*., 2018). The functional activation of TSN would be a novel mechanism causing the early carcinogenesis of cancer, which may be used to predict survival in cancer patients. In conclusion, the challenges in engineering TSN inhibitors in several studies suggested that plant-derived TSN proteins may be used as a diagnosis and prognostic biomarker in cancer therapy.

CONCLUSION

Bioactive peptides and proteins have emerged as important therapeutic agents thanks to their unique biochemical properties. This study, which utilized the application of bioinformatics tools and a literature search engine, identified five potential proteins related to cancer treatment procedures. Of those, Kunitz-trypsin type proteinase inhibitor, Dicer, and β-1,3-galactosyltransferase showed anti-tumor and anti-inflammatory activity, which could lead to the use of these bioactives in cancer prevention and treatment. In addition, cullin-4 and staphylococcal nuclease domain-containing proteins, which were overexpressed in tumor cells and associated with cell proliferation, may be used as a diagnosis and prognostic biomarker in cancer therapy. These therapeutic proteins may be considered important biomarkers for breeding selection and biotechnological development to define the targets for medicinal plant cultivation, domestication, and molecular pharming. However, further proteomics research requires more sample replications over plant genotypes to validate these conclusions.

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ETHICAL STATEMENT

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Bento, J.F., Noleto, G.R. & De Oliveira Petkowicz, C.L. 2014. Isolation of an arabinogalactan from Endopleura uchi bark decoction and its effect on HeLa cells. Carbohydrate Polymers, 101(1): 871–877. https://doi.org/10.1016/j.carbpol.2013.10.014

Blanco, M.A., Alečković, M., Hua, Y., Li, T., Wei, Y., Xu, Z., Cristea, I. M. & Kang, Y. 2011. Identification of staphylococcal nuclease domain-containing 1 (SND1) as a metadherin-interacting protein with metastasis-promoting functions. Journal of Biological Chemistry, 286(22): 19982–19992. https://doi.org/10.1074/jbc.M111.240077

Cheng, J., Guo, J., North, B.J., Tao, K., Zhou, P. & Wei, W. 2019. The emerging role for Cullin 4 family of E3 ligases in tumorigenesis. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer, 1871(1): 138–159. https://doi.org/10.1016/j.bbcan.2018.11.007

Chen, S.L., Yu, H., Luo, H.M., Wu, Q., Li, C.F. & Steinmetz, A. 2016. Conservation and sustainable use of medicinal plants: problems, progress, and prospects. Chinese Medicine, 11(37): 1–10. https://doi.org/10.1186/s13020-016-0108-7

Chin, A.R., Fong, M.Y., Somlo, G., Wu, J., Swiderski, P., Wu, X. & Wang, S.E. 2016. Cross-kingdom inhibition of breast cancer growth by plant miR159. Cell Research, 26(2): 217-228. https://doi.org/10.1038/cr.2016.13

Cid-Gallegos, M.S., Corzo-Ríos, L.J., Jiménez-Martínez, C. & Sánchez-Chino, X.M. 2022. Protease inhibitors from plants as therapeutic agents- A Review. Plant Foods for Human Nutrition, 77(1): 20–29. https://doi.org/10.1007/s11130-022-00949-4

Cijo, V., Dellaire, G. & Rupasinghe, H.P.V. 2017. Plant flavonoids in cancer chemoprevention: role

in genome stability. The Journal of Nutritional Biochemistry, 45: 1–14. https://doi.org/10.1016/j.jnutbio.2016.11.007

Cui, D., Xiong, X. & Zhao, Y. 2016. Cullin-RING ligases in regulation of autophagy. Cell Division, 11: 1-8. https://doi.org/10.1186/s13008-016-0022-5

De Filippis, L. & Magel, E. 2012. Identification of biochemical differences between the sapwood and transition zone in *Robinia pseudoacacia* L. by differential display of proteins. 66(4): 543–549. https://doi.org/doi:10.1515/hf.2011.178

Fukudome, A. & Fukuhara, T. 2017. Plant dicer-like proteins: double-stranded RNA-cleaving enzymes for small RNA biogenesis. Journal of Plant Research, 130(1): 33–44. https://doi.org/10.1007/s10265-016-0877-1

Gutierrez-Beltran, E., Denisenko, T.V., Zhivotovsky, B. & Bozhkov, P.V. 2016. Tudor staphylococcal nuclease: Biochemistry and functions. Cell Death and Differentiation, 23(11): 1739–1748. https://doi.org/10.1038/cdd.2016.93

Hu, X.Q., Han, W., Han, Z.Z., Liu, Q.X., Xu, X.K., Fu, P. & Li, H.L. 2014. A new macrocyclic lactone and a new quinoflavan from *Celastrus hindsii*. Phytochemistry Letters, 7: 169-172. https://doi.org/10.1016/j.phytol.2013.11.015

Iravani, S. & Varma, R.S. 2019. Plant-derived edible nanoparticles and miRNAs: Emerging frontier for therapeutics and targeted drug-delivery. ACS Sustainable Chemistry & Engineering, 7(9): 8055–8069. https://doi.org/10.1021/acssuschemeng.9b00954

Jang, S.M., Redon, C.E. & Aladjem, M.I. 2018. Chromatin-bound cullin-ring ligases: Regulatory roles in DNA replication and potential targeting for cancer therapy. Frontiers in Molecular Biosciences, 5(19). https://doi.org/10.3389/fmolb.2018.00019

Kerzendorfer, C., Hart, L., Colnaghi, R., Carpenter, G., Alcantara, D., Outwin, E., Carr, A.M. & O'Driscoll, M. 2011. CUL4B-deficiency in humans: Understanding the clinical consequences of impaired Cullin 4-RING E3 ubiquitin ligase function. Mechanisms of Ageing and Development, 132(8–9): 366–373. https://doi.org/10.1016/j.mad.2011.02.003

Kuo, Y.-H., Chen, C.F. & Kuo, L.M.Y. 1995. Celahinine a, a new sesquiterpene pyridine alkaloid from *Celastrus hindsii*. Journal of Natural Products, 58(11): 1735–1738. https://doi.org/10.1021/np50125a015

Lafarga, T., Acién-Fernández, F.G. & Garcia-Vaquero, M. 2020. Bioactive peptides and carbohydrates from seaweed for food applications: Natural occurrence, isolation, purification, and identification. Algal Research, 48: 101909. https://doi.org/10.1016/j.algal.2020.101909

Li, C.L., Yang, W.Z., Shi, Z. & Yuan, H.S. 2018. Tudor staphylococcal nuclease is a structure-specific ribonuclease that degrades RNA at unstructured regions during microRNA decay. RNA, 24:739-748. https://doi.org/10.1261/rna.064501.117

Ly, T.N., Shimoyamada, M. & Yamauchi, R. 2006. Isolation and characterization of rosmarinic acid oligomers in *Celastrus hindsii* Benth leaves and their antioxidative activity. Journal of Agricultural and Food Chemistry, 54(11): 3786–3793. https://doi.org/10.1021/jf052743f

Mohammadi, A., Mansoori, B. & Baradaran, B. 2017. Regulation of miRNAs by herbal medicine: An emerging field in cancer therapies. Biomedicine and Pharmacotherapy, 86: 262–270. https://doi.org/10.1016/j.biopha.2016.12.023

Nabih, H.K. 2020. Crosstalk between NRF2 and Dicer through metastasis regulating MicroRNAs; mir-34a, mir-200 family and mir-103/107 family. Archives of Biochemistry and Biophysics, 686: 108326. https://doi.org/10.1016/j.abb.2020.108326

Nakanishi, K. & Yoshikawa, N. 2016. Immunoglobulin A nephropathies in children (Includes HSP). In Pediatric Nephrology. https://doi.org/10.1007/978-3-662-43596-0

Ndeh, D. & Gilbert, H.J. 2018. Biochemistry of complex glycan depolymerisation by the human gut microbiota. FEMS Microbiology Reviews, 42(2): 146–164. https://doi.org/10.1093/femsre/fuy002

Nguyen, V.H., Pham, T.L., Ha, T.T.T. & Hoang, T.L.T. 2020a. Comparative proteomic analysis of *Celastrus hindsii* Benth. phenotypes reveals an intraspecific variation. Journal of Plant Biotechnology, 47(4): 273–282. https://doi.org/10.5010/JPB.2020.47.4.273

Nguyen, V.H., Pham, T.L. & Nguyen, Q.T. 2020b. Anti-oxidative metabolite comparison between two phenotypes of *Celastrus hindsii* Benth. Asian Journal of Agriculture and Biology, 8(4): 501–510. https://doi.org/10.35495/ajab.2020.04.223

Nosáľová, G., Prisenžňáková, L., Paulovičová, E., Capek, P., Matulová, M., Navarini, L. & Liverani, F. S. 2011. Antitussive and immunomodulating activities of instant coffee arabinogalactan-protein. International Journal of Biological Macromolecules, 49(4): 493–497. https://doi.org/10.1016/j.ijbiomac.2011.06.004

Otsuka, K., Yamamoto, Y., Matsuoka, R. & Ochiya, T. 2018. Maintaining good miRNAs in the body keeps the doctor away: Perspectives on the relationship between food-derived natural products and microRNAs in relation to exosomes/extracellular vesicles. Molecular Nutrition and Food Research, 62(1): 1–12. https://doi.org/10.1002/mnfr.201700080

Pham, T.N.A., Kim, H.L., Oh, S. & Yang, S.H. 2022. Anti-Inflammatory effects of the chemical compounds obtained from *Celastrus hindsii* in RAW264.7 cells. Microbiology and Biotechnology Letters, 50(1): 15–21. https://doi.org/10.48022/mbl.2111.11001

Roy, U.K., Lavignac, N., Rahman, A.M. & Nielsen, B.V. 2018. Purification of lectin and Kunitz trypsin inhibitor from soya seeds. Journal of Chromatographic Science, 56(5): 436-442. https://doi.org/10.1093/chromsci/bmy018

Rozov, S.M., Permyakova, N.V & Deineko, E.V. 2018. Main strategies of plant expression system glycoengineering for producing humanized recombinant pharmaceutical proteins. 83(3): 215-232. https://doi.org/10.1134/S0006297918030033

Scoparo, C.T., Souza, L.M., Dartora, N., Sassaki, G.L., Santana-Filho, A.P., Werner, M.F.P., Borato, D.G., Baggio, C.H. & Iacomini, M. 2016. Chemical characterization of heteropolysaccharides from green and black teas (*Camellia sinensis*) and their anti-ulcer effect. International Journal of Biological Macromolecules, 86: 772–781. https://doi.org/10.1016/j.ijbiomac.2016.02.017

Singh, N. & Sharma, A. 2017. Turmeric (*Curcuma longa*): miRNAs and their regulating targets are involved in development and secondary metabolite pathways. Comptes Rendus - Biologies, 340(11–12): 481–491. https://doi.org/10.1016/j.crvi.2017.09.009

Singh, N., Srivastava, S. & Sharma, A. 2016. Identification and analysis of miRNAs and their targets in ginger using bioinformatics approach. Gene, 575(2): 570–576. https://doi.org/10.1016/j.gene.2015.09.036

Taniya, M.S., MV, R., PS, S., Krishnan, G. & S, P. 2020. Bioactive peptides from amaranth seed protein hydrolysates induced apoptosis and antimigratory effects in breast cancer cells. Food Bioscience, 35: 100588. https://doi.org/10.1016/j.fbio.2020.100588

Tonolo, F., Folda, A., Cesaro, L., Scalcon, V., Marin, O., Ferro, S., Bindoli, A. & Rigobello, M.P. 2020. Milk-derived bioactive peptides exhibit antioxidant activity through the Keap1-Nrf2 signaling pathway. Journal of Functional Foods, 64: 103696. https://doi.org/10.1016/j.jff.2019.103696

Witwer, K.W. & Hirschi, K.D. 2014. Transfer and functional consequences of dietary microRNAs in vertebrates: Concepts in search of corroboration. BioEssays, 36(4): 394–406. https://doi.org/10.1002/bies.201300150

Xing, A., Pan, L. & Gao, J. 2018. p100 functions as a metastasis activator and is targeted by tumor suppressing microRNA-320a in lung cancer. Thoracic Cancer, 9(1): 152–158. https://doi.org/10.1111/1759-7714.12564

Yan, C., Yan, Z., Wang, Y., Yan, X. & Han, Y. 2014. Tudor-SN, a component of stress granules, regulates growth under salt stress by modulating GA20ox3 mRNA levels in *Arabidopsis*. Journal of Experimental Botany, 65(20): 5933–5944. https://doi.org/10.1093/jxb/eru334

Yu, L., Di, Y., Xin, L., Ren, Y., Liu, X., Sun, X., Zhang, W., Yao, Z. & Yang, J. 2017. SND1 acts as a novel gene transcription activator recognizing the conserved Motif domains of Smad promoters, inducing TGFβ1 response and breast cancer metastasis. Oncogene, 36(27): 3903–3914. https://doi.org/10.1038/onc.2017.30

Zahid, A., Despres, J., Benard, M., Nguema-Ona, E., Leprince, J., Vaudry, D., Rihouey, C., Vicré-Gibouin, M., Driouich, A. & Follet-Gueye, M.L. 2017. Arabinogalactan proteins from Baobab and Acacia seeds influence innate immunity of human keratinocytes *In vitro*. Journal of Cellular Physiology, 232(9): 2558–2568. https://doi.org/10.1002/jcp.25646

Zhou, J., Chen, M., Wu, S., Liao, X., Wang, J., Wu, Q., Zhuang, M. & Ding, Y. 2020. A review on mushroom-derived bioactive peptides: Preparation and biological activities. Food Research International, 134: 109230. https://doi.org/10.1016/j.foodres.2020.109230

Zhu, W. & Tan, S. 2017. Tudor-SN protein expression in colorectal cancer and its association with clinical characteristics. Open Life Sciences, 12(1): 237-242. https://doi.org/10.1515/biol-2017-0028