Agarwood

Subjects: Biotechnology & Applied Microbiology

Contributor: Pooja Shivanand , , Sarayu Krishnamoorthy

Agarwood, popularly known as oudh or gaharu, is a fragrant resinous wood of high commercial value, traded worldwide and primarily used for its distinctive fragrance in incense, perfumes, and medicine. This fragrant wood is created when Aquilaria trees are wounded and infected by fungi, producing resin as a defense mechanism. The depletion of natural agarwood caused by overharvesting amidst increasing demand has caused this fragrant defensive resin of endangered Aquilaria to become a rare and valuable commodity. Given that instances of natural infection are quite low, artificial induction, including biological inoculation, is being conducted to induce agarwood formation.

agarwood Aquilaria Market Value Bioactive Compounds

1. Natural Agarwood

Agarwood is formed when *Aquilaria* trees are wounded and exposed to biotic and abiotic stresses [1]. The infection triggers the trees' defense mechanism, causing resin to be produced, which aids the trees in suppressing the growth of the microbes infecting the trees in a process known as tylosis [1][2]. From the infection, the tree undergoes a biochemical reaction that produces oleoresin, which causes the color of the wood to eventually change from a lighter to a darker color, becoming what is commonly referred to as agarwood [1]. Wild-type agarwood takes years to produce, and few traders are willing to wait so long. Furthermore, only a small number of *Aquilaria* are infected in the wild and produce agarwood, and the only way to be certain that the tree contains the desired resin is to cut down the trees [3].

2. Artificially Induced Agarwood

Methods of artificial induction of agarwood have been created to prevent *Aquilaria* trees from becoming extinct. This causes the trees to become endangered, and, therefore, researchers have produced methods to artificially induce agarwood formation. There are three methods used: biological inoculation, chemical induction, and physical wounding.

2.1. Physical Wounding

Mechanical injuries are the common and traditional method used to induce agarwood formation, as it is cheap and is inexpensive, requiring no chemicals or reagents to be used. It is also much easier to teach methods of mechanical injuries to farmers who cultivate agarwood. In China, farmers in Hainan, Guangdong, and Yunnan

provinces were taught the physical wounding method to cultivate more than 20 million *A. sinensis* trees [4]. Ponjanagroon and Kaewrak [5] have used various methods of mechanical injuries on *A. crassna* to induce the production of agarwood; they inflicted wide and narrow wounds on the trees, made holes on the trees with screws of varied sizes, severe bark removal with hatchets, inserted nails of assorted sizes into the tree trunk, and the last one is to simply beat the *Aquilaria* trunk with a hammer. All methods produced discoloration; however, when the wood is burnt, the wood with nails hammered into the trunk gave no specific agarwood scent. Nobushi and Siripatanadilok [6] suggested that air and oxygen play a role in agarwood formation. Thus, when the nails are hammered into the trunk of the trees, oxygen is not able to enter the wound, and the discoloration around the wound could be caused by the reaction of ferric oxide in the nails and wood fibers [5]. Hence, there is no aromatic scent when burning the wood, as little or no resin was formed. The research also concluded that larger objects used to injure the trees cause wider discoloration, and the holes wounded with large screws were preferred, as it produces the classic agarwood scent when burnt and the quantity of agarwood at 20 months (about 1 and a half years)' harvest was still not enough for commercial purposes [5].

2.2. Biological Inoculation

Biological inoculation is also another alternative method to agarwood formation and has been proven by many researchers to help induce agarwood formation. It is necessary for the tree to first be wounded before it can be infected by microbes to induce agarwood formation. However, not all fungi can promote agarwood production; some of the species identified in agarwood-producing trees are *Fusarium*, *Lasiodiplodia*, *Penicillium*, and *Aspergillus*, amongst others [1]. Inoculation of endophytic fungi on *Aquilaria* trees has also been proven to produce resin in as fast as 6 months [7]. Chen et al. [8] studied the agarwood formation induced by fermentation liquid of different fungi, in which the fungi were isolated from a previously infected tree that produced agarwood and were inserted into the *Aquilaria* tree by using a transfusion set. It was found that the dominant fungi were *Lasiodiplodia theobromae*, which was present in all layers of the wood, followed by *Fusarium solani* [8]. This suggests that *L. theobromae* and *F. solani* have a significant role in agarwood production and are agarwood-promoting fungi.

2.3. Chemical Induction

Chemical induction is another common method of producing agarwood in many countries. It is common to use sulfuric acid, jasmonic acid, acetic acid, and alcohol to induce agarwood formation, of which jasmonic acid has been proven to induce agarwood formation by 2–3 mm (about 0.12 in) thickness in Vietnam [9]. However, some countries have used sulfuric acid and acetic acid with unsuccessful results, and some chemicals are toxic to humans, hence the importance of choosing the proper chemicals when the agarwood is intended to be used for making perfumes, tea, and medicines [9]. Methods for injecting the chemicals in agarwood are similar in many reports, in which a hole is drilled into the trunk of the tree, and the chemicals are injected into the tree using a syringe or transfusion set [4][9][10]). There are kits and techniques made by researchers to induce agarwood production, such as the cultivated agarwood kits (CA-Kits) developed by Prof. Blanchette from the University of Minnesota, Vietnam, the whole-tree agarwood-inducing technique (Agar-Wit) that was developed in China [4]), and the agarwood inducement method (AINM) developed by Nuclear Malaysia, in which small holes of about 50 cm are

drilled into the xylem of a tree followed by injection of agarwood inducers into the xylem. The resin can then be harvested after 6 months [10].

3. Bioactive Compounds Obtained from Agarwood, Their Pharmaceutical Properties, and Medicinal Benefits

Agarwood and its products, either as oil, smoke, or powder admixtures, are well known for their bioactivity in controlling various fungal pathogens and their unique medicinal properties globally [11]. Several chemical compounds have been reported to be identified from agarwood such as chromone derivates, terpenoids, flavonoids, benzophenones, lignans, benzenoid derivates, phenolic compounds, triterpenes, steroids, and other chemical compounds [12][13]. Of these, chromones and terpenoids (sesquiterpenoids) are the compounds of interest that are potentially known for their bioactivity, pharmaceutical value, and medicinal properties [13]. In contrast, the other chemical compounds are natural compounds observed in most plants and trees [14].

3.1. Chromones

More than 80 different chromones (2-(2-phenylethyl) chromones) and about 31 different terpenoids are known to date that are responsible for various medicinal benefits [15]. Chromones (1,4-benzopyrone) are the known isomer of coumarin, which are derivatives of benzopyran with a substituted keto group in the pyran ring, are ubiquitously present in the Pant Kingdom, and are a part of the human and animal diet [16]. The 2-(2-phenylethyl) chromones are the rare and uncommon group of chromones that possess phenylethylene at the C-2 position, which are reported to be abundantly available in agarwood resin [17][18]. These 2-(2-phenylethyl) chromones have been isolated only from a few plant species, making it a rare compound extracted from plants such as agarwood that are responsible for the warm, balsamic, long-lastingly sweet odor of the burnt agarwood [19]. Furthermore, they are classified into four subgroups, namely 2-(2-Phenylethyl)chromone monomers (PEC), comprising four subdivisions (Flindersia-type 2-(2-phenylethyl)chromones, the most abundant group; 5,6,7,8-Tetrahydro-2-(2-phenylethyl)chromones, highly oxidizing group; mono-epoxy-5,6,7,8-tetrahydro-2-(2-phenylethyl)chromones; diepoxy-5,6,7,8-tetrahydro-2-(2-henylethyl)chromones), 2-(2-Phenylethenyl)chromones are predominantly obtained from chemical synthesis, agarwood, cyanobacteria, and rhizomes of *Imperata cylindrica* or *Platanus x acerifolia*; dimeric 2-(2-phenylethyl)chromones; sesquiterpenoid-4H-chromones and benzylacetone-4H-chromones, predominantly obtained from *Gyrinops salicifolia*; and trimeric 2-(2-phenethyl)chromones [20][21][22][23][24][25]. They act as potential and remarkable pharmacological compounds containing various bioactivities such as antimicrobial, antiviral, anticancer, antitumor, anti-inflammatory, antioxidant, enzyme inhibition, antifeedant, antidepressant, antiobesity, and antihypersensitive properties, including antagonistic activity in melanin-concentrating hormone receptor-1 [26][27][28].

Furthermore, chromones are considered naturally available products with diverse structures and functions that act as potential candidates for replacing synthetic drugs in various pharmacological therapeutics [27][29][30][31][32][33][34][35][36][37][38][39][40][41][42]. Similarly, Duan et al. [43] and Vanguru et al. [44] have reported the therapeutic properties of chromones against a wide range of cancers, especially in controlling breast cancer and ovarian cancer [45][46]. They

act as intercellular adhesion molecule inhibitors, cyclooxygenase inhibitors, mast cell stabilizers, leukotriene receptor antagonists, interleukin-5 inhibitors, lipoxygenase inhibitors, and nitric oxide production inhibitors controlling inflammation as potential anti-inflammatory compounds [47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63]. Chromones derived from the leaf extracts of plants act as the basic structural compound in the development of various drugs that inhibit infectious diseases caused by a wide range of microbes inferring its antimicrobial property [64][65][66][67][68]. Reactive oxygen species (ROS) act as oxygen moieties impairing the DNA, lipids, proteins, and lipoproteins with their oxidative damage [69][70][71]. Chromones present in the food material (plants) act as potential antioxidants in reducing the lipid peroxidase activity of the ROS and free radicals and disease progression [72][73][74][75][76][77][78][79]. In particular, chromones have been found to be promising in controlling and treating the neurodegenerative disease Alzheimer's, which is caused due to the redox imbalance created by the free radicals and the ROS in the human brain [80][81]. Valentina et al. [82] and Wang et al. [83] have investigated and reported the inhibitory effect of the chromones on the α-amylase and α-glucosidase enzymes to manage postprandial diabetes by delaying sugar uptake in the human body. Further, the role of chromones in the treatment of various disorders such as gastritis, diarrhea, stiff muscles, hypothermic disease, diuretic disease, nephritis, cystitis, pyrexia, rheumatism, headache, hepatitis, cough, bronchitis, asthma, etc. have been reported and described by various researchers worldwide [26][27][28].

3.2. Terpenoids

Terpenoids are abundantly present in nature, especially in plants, and are known to contain oxygen derivatives that bear a hydroxyl group at the C-3 position [14]. To date, about three different terpenoids have been identified in agarwood and *Aquilaria* plant leaves, namely 3-oxo-22-hydroxyhopane, 3b-olean-12-ene-3,23-diol, and hederagenin [5][84][85]. Among all the terpenoids known, sesquiterpenoids are the dominant fragrant compounds observed to be present in agarwood and agarwood products with the presence of three isoprene structural units [19][86]. They exist as volatile compounds in the essential oils extracted from agarwood and are of several types with unique aromatic properties specific to each type [14]. Eudesmanes, otherwise known as selinanes, are bicyclic sesquiterpenoids with a decalin skeleton, diverse functional groups, and multiple chiral centers acting as significant sesquiterpenoids found in agarwood obtained from *Aquilaria agallocha, A. sinensis, A. crassna, A. malaccensis,* and *Gyrinops salicifolia* [5][22][24][87][88][89]. They possess a sweet, woody, honey, balsamic, minty, and fresh floral odor [19]. Guaianes are the sesquiterpenoids made of a five- and seven-membered ring-coupled structures containing 4,10-dimethyl-7-isopropenyl moiety and are observed in *Aquilaria* and *Gyrinops* species with a woody and floral odor [22][85][90][91]. Agarospiranes sesquiterpenes, also known as vetispiranes, are composed of spirocyclic sesquiterpenes present in *Aquilaria agallocha, A. sinensis, A. crassna,* and *A. malaccensis* with a spicy, peppery, woody, sweet, and balsamic odor [19][91][92][93]. Eremophilanes, known as valencanes, are similar to eudesmanes structurally and differ due to the presence of a specific methyl group in the structure with a characteristic warm woody and minty odor [5][22][24]. Acoranes, responsible for the long-lasting odor of agarwood, are the spiro sesquiterpenes that are rarely obtained from agarwood [85][87][94]. Cadinanes, a bicyclic sesquiterpene, is similar to eudesmanes with the presence of an isopropyl and methyl group in its structure obtained from *A. sinensis* and *A. crassna* [5][95]. Prezizaanes are the tricyclic sesquiterpenes found in *A. malaccensis* with a special fragrance [94][96][97]. Similarly, Zizaanes, a tricyclic, and Humulanes, a humulane-type

sesquiterpenes, have also been reported to be obtained from *A. sinensis and A. crassna* [87][94][98]. Further, other sesquiterpenoids such as daphnauranols obtained from *A. malaccensis*, 12-Hydroxy-dihydrocyperolone from *G. salicifolia*, malacinones A and B from *A. malaccensis*, and 1,5,9-trimethyl-1,5,9-cyclododecatriene from *A. sinensis* have been reported by researchers such as Ma et al. [98], Li et al. [85], Chen et al. [99], and Ma et al. [100]. Among all the sesquiterpenoids reported, eudesmanes, eremophilanes, and guaianes are the potential sesquiterpenoids obtained from agarwood of which guaianes are the compounds possessing high structural diversity that are specific to each plant species [14].

Furthermore, sesquiterpenes act as a potential neuroprotective agent and help in combating Alzheimer's disease [101]. Similarly, agarol obtained from *A. malaccensis*, an eudesmane sesquiterpene, and 8bH-Dihydrogmelofuran and gmelofuran, a cadinene sesquiterpenes isolated from *A. malaccensis* and *A. agallocha*, were reported to have anticancer, antioxidant and antimicrobial properties [102]. Antidiabetes activity has been observed in some sesquiterpenoids such as Prezizaane, jinkohol II, aquilarene D, jinkohol, zizaane, agarozizanol E, and isokhusenol acting as inhibitors against α-glucosidase [103].

Moreover, cucurbitacin triterpenoids were found to possess cytotoxic activities, making them a potential candidate for the treatment of cancer [104]. Similarly, β-Caryophyllene, isolated from *A. crassna*, was found to specifically help in the de-proliferation of cancerous cells. Further, β-Caryophyllene was a potential antimicrobial compound effective against various pathogenic strains that include *Bacillus cereus, B. subtilis, S. aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Aspergillus niger, Penicillium citrinum, Rhizopus oryzae,* and *Trichoderma reesei* [102]. Flavonoids, benzophenones, xanthones, lignans, phenolic compounds, degraded sesquiterpenes, alkaloids, and nucleosides are some of the other chemical constituents of the *Aquilaria* species that are available compounds in plants, and they contribute to the structural stability of the plants [12].

4. Economic Importance and Market Value of Agarwood

Aquilaria trees and the agarwood obtained from them are very popular for the wide variety of economically important products obtained from them [105]. Their products, such as wood, wood chips, oil, powder, and flakes, have been used in various applications such as medicinal, religious, cosmetics, and cultural purposes [106][107]. Antonopoulou et al. [108], Barden et al. [109], Kiet [110], Lim and Anack [111], Persoon [112], and Sitepu et al. [113] have reported the potential usage of agarwood oil and powder in Ayurvedic medicine practiced in the Indian subcontinent, and also in Tibetan, Vietnamese, Chinese, and Malaysian medicines. Moreover, it is used for religious and cultural purposes in many countries such as Northeast and Southeast Asia, Taiwan, Korea, and Japan [107][108][114]. Furthermore, Sitepu et al. [113], Barden et al. [109], and Chakrabarty et al. [115] have reported the importance of agarwood in the manufacturing of perfumes, cosmetic products, soaps, shampoos, incense, and other fragrance products worldwide.

Therefore, the market value of agarwood and the demand for its products have increased tremendously. Globally, agarwood products, such as wood pieces, wood chips, powder, oil, dust, incense, and perfumes, have been reported to have a market value of USD several thousand billion [105][109][116]. Agarwood is graded into different

categories based on the resin quality; the first grade has a high global demand increasing the market value to about USD 10,000 per kg of wood, and the least grade with USD 30 per kg [117]. Further, according to a report by Nanyang Siang Pau in 2005 and Abdin [118], agarwood oil is generally sold at a cost of USD 30,000 to 40,000 per kg. Similarly, in 2013, Akter et al. [2] reported an estimated increase in the market value of agarwood and its products to reach up to USD 6–8 billion or even up to USD 36 billion by 2017. Similarly, other reports from various sources indicate that the agarwood oil market value is expected to reach about USD 201.03 million by 2026. Hence, it is essential to better understand the basic scientific concepts of agarwood induction and formation to improve its production. Furthermore, the invention of simple technology for induction would enable the easy handling of the techniques by farmers to induce the crops.

References

1. Sangareswari, M.; Parthiban, K.T.; Kanna, S.U.; Karthiba, L.; Saravanakumar, D. Fungal Microbes Associated with Agarwood Formation. Am. J. Plant Sci. 2016, 7, 1445–1452.
2. Akter, S.; Islam, T.; Zulkefeli, M.; Khan, S.I. Agarwood Production–A Multidisciplinary Field to be Explored in Bangladesh. Int. J. Pharm. Life Sci. 2013, 2, 22–32.
3. Persoon, G.A. Agarwood: The Life of a Wounded Tree. In Proceedings of the 2nd International Agarwood Conference, Bangkok/Koh Chang, Thailand, 4–11 March 2007; IIAS: Leiden, The Netherlands, 2007.
4. Liu, Y.; Chen, H.; Yang, Y.; Zhang, Z.; Wei, J.; Meng, H.; Chen, W.; Feng, J.; Gan, B.; Chen, X.; et al. Whole-tree Agarwood-Inducing Technique: An Efficient Novel Technique for Producing High-Quality Agarwood in Cultivated Aquilaria sinensis Trees. Molecules 2013, 18, 3086–3106.
5. Pojanagaroon, S.; Kaewrak, C. Mechanical Methods to Stimulate Aloes Wood Formation in Aquilaria crassna Pierre Exhlec. (Kritsana) Trees. Acta Hortic. 2005, 161–166.
6. Nobuchi, T.; Siripatanadilok, S. Preliminary observation of Aquilaria crassna wood associated with the formation of aloeswood. Bull. Kyoto Univ. For. 1991, 63, 226–235.
7. Jong, P.L.; Tsan, P.; Mohamed, R. Gas chromatography–mass spectrometry analysis of agarwood extracts from mature and juvenile Aquilaria malaccensis. Int. J. Agric. Biol. 2014, 16, 644–648.
8. Chen, X.; Liu, Y.; Yang, Y.; Feng, J.; Liu, P.; Sui, C.; Wei, J. Trunk surface agarwood-inducing technique with Rigidoporus vinctus: An efficient novel method for agarwood production. PLoS ONE 2018, 13, e0198111.
9. Turjaman, M.; Hidayat, A.; Santoso, E. Development of Agarwood Induction Technology Using Endophytic Fungi. In Agar-wood; Tropical Forestry; Mohamed, R., Ed.; Springer: Berlin, Germany; Singapore, 2016; pp. 57–71.

10. Chong, S.P.; Osman, M.F.; Bahari, N.; Nuri, E.A.; Zakaria, R.; Abdul Rahim, K. Agarwood inducement technology: A method for producing oil grade agarwood in cultivated Aquilaria malaccensis. Lamk J. Agrobiotech. 2015, 6, 1–16.
11. Hidayat, A.; Turjaman, M.; Qamyari, R.; Imanuddin, R.; Tohir, D.; Rahmanto, R.G.H.; Susilowati, A. Bioactive composition, antifungal, antioxidant, and anticancer potential of agarwood essential oil from decaying logs (Gyrinops spp.) of Papua Island (Indonesia). J. Appl. Pharm. Sci. 2021, 11, 70–78.
12. Tan, C.S.; Isa, N.; Ismail, I.; Zainal, Z. Agarwood Induction: Current Developments and Future Perspectives. Front. Plant Sci. 2019, 10, 122.
13. Yuan, H.W.; Zhao, J.P.; Liu, Y.B.; Qiu, Y.X.; Xie, Q.L.; Li, M.J.; Khan, I.A.; Wang, W. Advance in studies on chemical constituents, pharmacology and quality control of Aquilaria sinensis. Digit. Chin. Med. 2018, 1, 316–330.
14. Li, W.; Chen, H.-Q.; Wang, H.; Mei, W.-L.; Dai, H.-F. Natural products in agarwood and Aquilaria plants: Chemistry, biological activities and biosynthesis. Nat. Prod. Rep. 2020, 38, 528–565.
15. Wang, S.L.; Hwang, T.L.; Chung, M.I.; Sung, P.J.; Shu, C.W.; Cheng, M.J.; Chen, J.J. New flavones, a 2-(2-phenylethyl)-4H-chromen-4-one derivative, and anti-inflammatory constituents from the stem barks of Aquilaria sinensis. Molecules 2015, 20, 20912–20925.
16. Cock, I.E. The Genus Aloe: Phytochemistry and Therapeutic Uses Including Treatments for Gastrointestinal Conditions and Chronic Inflammation. In Novel Natural Products: Therapeutic Effects in Pain, Arthritis and Gastro-Intestinal Diseases; Rainsford, K., Powanda, M., Whitehouse, M., Eds.; Springer: Basel, Switzerland, 2015; Volume 70, pp. 179–235.
17. Liu, Y.Y.; Chen, D.L.; Yu, Z.X.; Can-Hong, W.; Feng, J.; Meng, Y.; Wei, J.H. New 2-(2-phenylethyl)chromone derivatives from agarwood and their inhibitory effects on tumor cells. Nat Prod Res. 2020, 34, 1721–1727.
18. Huo, H.X.; Zhu, Z.X.; Song, Y.L.; Shi, S.P.; Sun, J.; Sun, H.; Zhao, Y.F.; Zheng, J.; Ferreira, D.; Zjawiony, J.K.; et al. Anti-inflammatory dimeric 2-(2-phenylethyl) chromones from the resinous wood of Aquilaria sinensis. J. Nat. Prod. 2017, 81, 543–553.
19. Naef, R. The volatile and semi-volatile constituents of agarwood, the infected heartwood of Aquilaria species: A review. Flavour Fragr. J. 2011, 26, 73–87.
20. Liao, G.; Dong, W.-H.; Yang, J.-L.; Li, W.; Wang, J.; Mei, W.-L.; Dai, H.-F. Monitoring the Chemical Profile in Agarwood Formation within One Year and Speculating on the Biosynthesis of 2-(2-Phenylethyl)Chromones. Molecules 2018, 23, 1261.
21. Wang, S.; Yu, Z.; Wang, C.; Wu, C.; Guo, P.; Wei, J. Chemical Constituents and Pharmacological Activity of Agarwood and Aquilaria Plants. Molecules 2018, 23, 342.

22. Shao, H.; Kong, F.D.; Wang, H.; Mei, W.L.; Dai, H.F. Qinanmer, a new compound from chinese agarwood ‘Qi-nan’ originating from Aquilaria sinensis. J. Asian Nat. Prod. Res. 2017, 19, 935–940.
23. Kuang, T.D.; Chen, H.Q.; Kong, F.D.; Cai, C.H.; Yang, L.; Mei, W.L.; Dai, H.F. UPLC-MS-guided isolation of single ether linkage dimeric 2-(2-phenylethyl)chromones from Aquilaria sinensis Phytochem. Lett. 2018, 26, 96–100.
24. Wu, B.; Kwon, S.W.; Hwang, G.S.; Park, J.H. Eight New 2-(2-Phenylethyl)chromone (=2-(2-Phenylethyl)-4H-1-benzopyran-4-one) Derivatives from Aquilaria malaccensis Agarwood. Helvetica Chim. Acta 2012, 95, 1657–1665.
25. Liu, J.M.; Gao, Y.H.; Xu, H.H.; Xu, Z.Q. Chemical constituents of Lignum Aquilariae Resinatum (II). Chin. Tradit. Herb. Drugs 2007, 38, 1138–1140.
26. Sharma, S.K.; Kumar, S.; Chand, K.; Kathuria, A.; Gupta, A.; Jain, R. An update on natural occurrence and biological activity of chromones. Curr. Med. Chem. 2011, 18, 3825–3852.
27. Nazhand, A.; Durazzo, A.; Lucarini, M.; Romano, R.; Mobilia, M.A.; Izzo, A.A.; Santini, A. Human health-related properties of chromones: An overview. Nat. Prod. Res. 2019, 34, 137–152.
28. Kulshrestha, A.; Rupanwal, R.; Singh, N.; Panhekar, D.; Ey, J. Therapeutic Potential of Chromones. Int. J. Chem. Sci. 2017, 15, 200.
29. Abenavoli, L.; Izzo, A.A.; Milic, N.; Cicala, C.; Santini, A.; Capasso, R. Milk thistle (Silybum marianum): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases. Phytother. Res. 2018, 32, 2202–2213.
30. Andrew, R.; A Izzo, A. Principles of pharmacological research of nutraceuticals. J. Cereb. Blood Flow Metab. 2017, 174, 1177–1194.
31. Ruggeri, M.; Coretti, S.; Prete, S.; Romano, F.; Orlando, V.; Codella, P.; Di Brino, E. Economic evaluation of screening programs for hepatitis C virus infection: Evidence from literature. Risk Manag. Health Policy 2015, 8, 45–54.
32. Daliu, P.; Santini, A.; Novellino, E. A decade of nutraceutical patents: Where are we now in 2018? Expert Opin. Ther. Pat. 2018, 28, 875–882.
33. Daliu, P.; Santini, A.; Novellino, E. From pharmaceuticals to nutraceuticals: Bridging disease prevention and management. Expert Rev. Clin. Pharmacol. 2018, 12, 1–7.
34. Durazzo, A.; D’Addezio, L.; Camilli, E.; Piccinelli, R.; Turrini, A.; Marletta, L.; Marconi, S.; Lucarini, M.; Lisciani, S.; Gabrielli, P.; et al. From Plant Compounds to Botanicals and Back: A Current Snapshot. Molecules 2018, 23, 1844.
35. Durazzo, A.; Lucarini, M.; Souto, E.B.; Cicala, C.; Caiazzo, E.; Izzo, A.A.; Novellino, E.; Santini, A. Polyphenols: A concise overview on the chemistry, occurrence, and human health. Phytother.

Res. 2019, 33, 2221–2243.

36. Kumari, A.; Singh, R.K. Medicinal chemistry of indole derivatives: Current to future therapeutic prospectives. Bioorg. Chem. 2019, 89, 103021.
37. Menditto, E.; Cahir, C.; Aza-Pascual-Salcedo, M.; Bruzzese, D.; Poblador-Plou, B.; Malo, S.; Costa, E.; Gonzalez-Rubio, F.; Gimeno-Miguel, A.; Orlando, V.; et al. Adherence to chronic medication in older populations: Application of a common protocol among three European cohorts. Patient Prefer. Adherence 2018, 12, 1975–1987.
38. Salehi, B.; Armstrong, L.; Rescigno, A.; Yeskaliyeva, B.; Seitimova, G.; Beyatli, A.; Sharmeen, J.; Mahomoodally, M.F.; Sharopov, F.; Durazzo, A.; et al. Lamium Plants—A Comprehensive Review on Health Benefits and Biological Activities. Molecules 2019, 24, 1913.
39. Salehi, B.; Venditti, A.; Sharifi-Rad, M.; Kręgiel, D.; Sharifi-Rad, J.; Durazzo, A.; Lucarini, M.; Santini, A.; Souto, E.B.; Novellino, E.; et al. The Therapeutic Potential of Apigenin. Int. J. Mol. Sci. 2019, 20, 1305.
40. Santini, A.; Novellino, E. Nutraceuticals: Beyond the diet before the drugs. Curr. Bioact. Compd. 2014, 10, 1–12.
41. Santini, A.; Tenore, G.C.; Novellino, E. Nutraceuticals: A paradigm of proactive medicine. Eur. J. Pharm. Sci. 2017, 96, 53–61.
42. Scala, D.; Menditto, E.; Armellino, M.F.; Manguso, F.; Monetti, V.M.; Orlando, V.; Antonino, A.; Makoul, G.; De Palma, M. Italian translation and cultural adaptation of the communication assessment tool in an outpatient surgical clinic. BMC Health Serv. Res. 2016, 16, 1–7.
43. Duan, Y.-D.; Jiang, Y.-Y.; Guo, F.-X.; Chen, L.-X.; Xu, L.-L.; Zhang, W.; Liu, B. The antitumor activity of naturally occurring chromones: A review. Fitoterapia 2019, 135, 114–129.
44. Vanguru, M.; Merugu, R.; Garimella, S.; E, L. A Review on the Synthetic Methodologies of Chromones. Asian J. Pharm. Clin. Res. 2018, 11, 9–16.
45. Meydani, A.; Yousefi, S.; Gharibi, R.; Kazemi, S.; Teimouri, M.B. Synthesis of a new series of furopyranone- and furocoumarin-chromone conjugates followed by in–vitro cytotoxicity activity evaluation, and molecular docking study. Chem. Sel. 2019, 4, 3315–3324.
46. Elsayed, S.A.; Butler, I.S.; Claude, B.J.; Mostafa, S.I. Synthesis, characterization and anticancer activity of 3-formylchromone benzoylhydrazone metal complexes. Transit. Met. Chem. 2014, 40, 179–187.
47. Chen, D.; Xu, Z.; Chai, X.; Zeng, K.; Jia, Y.; Bi, D.; Ma, Z.; Tu, P. Nine 2-(2-Phenylethyl)chromone Derivatives from the Resinous Wood of Aquilaria sinensis and Their Inhibition of LPS-Induced NO Production in RAW 264. 7 Cells. Eur. J. Org. Chem. 2012, 2012, 5389–5397.

48. Gautam, R.; Jachak, S.M.; Kumar, V.; Mohan, C.G. Synthesis, biological evaluation and molecular docking studies of stellatin derivatives as cyclooxygenase (COX-1, COX-2) inhibitors and anti-inflammatory agents. Bioorg. Med. Chem. Lett. 2011, 21, 1612–1616.
49. Jachak, S.M.; Gautam, R.; Selvam, C.; Madhan, H.; Srivastava, A.; Khan, T. Anti-inflammatory, cyclooxygenase inhibitory and antioxidant activities of standardized extracts of Tridax procumbens L. Fitoterapia 2011, 82, 173–177.
50. Singh, A.; Kaur, M.; Sharma, S.; Bhatti, R.; Singh, P. Rational design, synthesis and evaluation of chromone-indole and chromone-pyrazole based conjugates: Identification of a lead for anti-inflammatory drug. Eur. J. Med. Chem. 2014, 77, 185–192.
51. Joo, C.; Venkateswararao, E.; Lee, K.-C.; Sharma, V.K.; Kyung, M.-S.; Kim, Y.; Jung, S.-H. Novel interleukin-5 inhibitors based on hydroxyethylaminomethyl-4H-chromen-4-one scaffold. Bioorg. Med. Chem. 2012, 20, 5757–5762.
52. Thanigaimalai, P.; Le Hoang, T.A.; Lee, K.-C.; Sharma, V.K.; Bang, S.-C.; Yun, J.H.; Roh, E.; Kim, Y.; Jung, S.-H. Synthesis and evaluation of novel chromone analogs for their inhibitory activity against interleukin-5. Eur. J. Med. Chem. 2010, 45, 2531–2536.
53. Venkateswararao, E.; Kim, M.-S.; Sharma, V.K.; Lee, K.-C.; Subramanian, S.; Roh, E.; Kim, Y.; Jung, S.-H. Identification of novel chromenone derivatives as interleukin-5 inhibitors. Eur. J. Med. Chem. 2013, 59, 31–38.
54. Venkateswararao, E.; Manickam, M.; Boggu, P.; Kim, Y.; Jung, S.-H. Exploration of benzamidochromenone derivatives with conformational restrictor as interleukin-5 inhibitors. Bioorg. Med. Chem. 2015, 23, 2498–2504.
55. Altavilla, D.; Squadrito, F.; Bitto, A.; Polito, F.; Burnett, B.; Di Stefano, V.; Minutoli, L. Flavocoxid, a dual inhibitor of cyclooxygenase and 5-lipoxygenase, blunts pro-inflammatory phenotype activation in endotoxin-stimulated macrophages. J. Cereb. Blood Flow Metab. 2009, 157, 1410–1418.
56. Ribeiro, D.; Freitas, M.; Tomé, S.M.; Silva, A.M.; Porto, G.; Cabrita, E.J.; Marques, M.M.B.; Fernandes, E. Inhibition of LOX by flavonoids: A structure–activity relationship study. Eur. J. Med. Chem. 2013, 72, 137–145.
57. An, H.-J.; Nugroho, A.; Song, B.-M.; Park, H.-J. Isoeugenin, a Novel Nitric Oxide Synthase Inhibitor Isolated from the Rhizomes of Imperata cylindrica. Molecules 2015, 20, 21336–21345.
58. Förstermann, U.; Sessa, W.C. Nitric oxide synthases: Regulation and function. Eur. Heart J. 2012, 33, 829–837.
59. Gao, H.-Y.; Wang, H.-Y.; Li, G.-Y.; Du, X.-W.; Zhang, X.-T.; Han, Y.; Huang, J.; Li, X.-X.; Wang, J.-H. Constituents from Zhuyeqing Liquor and their inhibitory effects on nitric oxide production. Phytochem. Lett. 2013, 7, 150–155.

60. Jia, B.-X.; Zeng, X.-L.; Ren, F.-X.; Jia, L.; Chen, X.-Q.; Yang, J.; Liu, H.-M.; Wang, Q. Baeckeins F–I, four novel C-methylated biflavonoids from the roots of Baeckea frutescens and their anti-inflammatory activities. Food Chem. 2014, 155, 31–37.
61. Kim, Y.A.; Kong, C.-S.; Park, H.H.; Lee, E.; Jang, M.-S.; Nam, K.-H.; Seo, Y. Anti-Inflammatory Activity of Heterocarpin from the Salt Marsh Plant Corydalis heterocarpa in LPS-Induced RAW 264. 7 Macrophage Cells. Molecules 2015, 20, 14474–14486.
62. Liu, G.-B.; Xu, J.-L.; Geng, M.; Xu, R.; Hui, R.-R.; Zhao, J.-W.; Xu, Q.; Xu, H.-X.; Li, J.-X. Synthesis of a novel series of diphenolic chromone derivatives as inhibitors of NO production in LPS-activated RAW264. 7 macrophages. Bioorg. Med. Chem. 2010, 18, 2864–2871.
63. Pham, T.-A.; Che, H.; Phan, P.-T.; Lee, J.-W.; Kim, S.-S.; Park, H. Oroxylin A analogs exhibited strong inhibitory activities against iNOS-mediated nitric oxide (NO) production. Bioorg. Med. Chem. Lett. 2012, 22, 2534–2535.
64. Cano, P.A.; Islas-Jacome, A.; Rangel-Serrano, A.; Anaya-Velazquez, F.; Padilla-Vaca, F.; Trujillo-Esquivel, E.; Ponce-Noyola, P.; Martinez-Richa, A.; Gamez-Montano, R. In vitro studies of chromonetetrazoles against pathogenic protozoa, bacteria, and fungi. Molecules 2015, 20, 12436–12449.
65. He, J.; Li, Z.-H.; Ai, H.-L.; Feng, T.; Liu, J.-K. Anti-bacterial chromones from cultures of the endophytic fungus Bipolaris eleusines. Nat. Prod. Res. 2018, 33, 3515–3520.
66. Hiruy, M.; Bisrat, D.; Mazumder, A.; Asres, K. Two chromones with antimicrobial activity from the leaf latex of Aloe monticola Reynolds. Nat. Prod. Res. 2019, 35, 1052–1056.
67. Li, G.-Y.; Li, B.-G.; Yang, T.; Liu, G.-Y.; Zhang, G.-L. Secondary Metabolites from the Fungus Chaetomium brasiliense. Helvetica Chim. Acta 2008, 91, 124–129.
68. Huang, J.-Q.; Liao, Y.-C.; Chen, H.-J.; Zhang, Z. Chemical solution is an efficient method to induce the formation of 2-(2-phenylethyl) chromone derivatives in Aquilaria sinensis. Phytochem. Lett. 2017, 19, 64–70.
69. Durazzo, A. Study Approach of Antioxidant Properties in Foods: Update and Considerations. Foods 2017, 6, 17.
70. Durazzo, A. Extractable and Non-extractable polyphenols: An overview. In Non-extractable Polyphenols and Carotenoids: Importance in Human Nutrition and Health (Food Chemistry, Function and Analysis, Volume 5); Saura-Calixto, F., Perez-Jimenez, J., Eds.; The Royal Society of Chemistry: London, UK, 2018.
71. Durazzo, A.; Lucarini, M. Extractable and Non-Extractable Antioxidants. Molecules 2019, 24, 1933.

72. Grazul, M.; Kufelnicki, A.; Wozniczka, M.; Lorenz, I.-P.; Mayer, P.; Jozwiak, A.; Czyz, M.; Budzisz, E. Synthesis, structure, electrochemical properties, cytotoxic effects and antioxidant activity of 5-amino-8-methyl-4H-benzopyran-4-one and its copper (II) complexes. Polyhedron 2012, 31, 150–158.
73. Kang, J.; Sun, J.-H.; Zhou, L.; Ye, M.; Han, J.; Wang, B.-R.; Guo, D.-A. Characterization of compounds from the roots of Saposhnikovia divaricata by high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry. Rapid Commun. Mass Spectrom. 2008, 22, 1899–1911.
74. Kuroda, M.; Uchida, S.; Watanabe, K.; Mimaki, Y. Chromones from the tubers of Eranthis cilicica and their antioxidant activity. Phytochemistry 2009, 70, 288–293.
75. Park, Y.J.; Kim, H.J.; Lee, S.J.; Choi, H.-Y.; Jin, C.; Lee, Y.S. A New Chromone, 11-Hydroxy-sec-O-glucosylhamaudol from Ostericum koreanum. Chem. Pharm. Bull. 2007, 55, 1065–1066.
76. Phosrithong, N.; Samee, W.; Nunthanavanit, P.; Ungwitayatorn, J. In Vitro Antioxidant Activity Study of Novel Chromone Derivatives. Chem. Biol. Drug Des. 2012, 79, 981–989.
77. Proença, C.; Albuquerque, H.M.T.; Ribeiro, D.; Freitas, M.; Santos, C.M.M.; Silva, A.M.S.; Fernandes, E. Novel chromone and xanthone derivatives: Synthesis and ROS/RNS scavenging activities. Eur. J. Med. Chem. 2016, 115, 381–392.
78. Yimam, M.; Brownell, L.; Jia, Q. Aloesin as a medical food ingredient for systemic oxidative stress of diabetes. World J. Diabetes 2015, 6, 1097–1107.
79. Csepanyi, E.; Szabados-Furjesi, P.; Kiss-Szikszai, A.; Frensemeier, L.M.; Karst, U.; Lekli, I.; Haines, D.D.; Tosaki, A.; Bak, I. Antioxidant Properties and Oxidative Transformation of Different Chromone Derivatives. Molecules 2017, 22, 588.
80. Reis, J.; Gaspar, A.; Milhazes, N.; Borges, F. Chromone as a Privileged Scaffold in Drug Discovery: Recent Advances. J. Med. Chem. 2017, 60, 7941–7957.
81. Demetgül, C.; Beyazit, N. Synthesis, characterization and antioxidant activity of chitosan-chromone derivatives. Carbohydr. Polym. 2018, 181, 812–817.
82. Valentina, P.; Ilango, K.; Chander, S.; Murugesan, S. Design, synthesis and α-amylase inhibitory activity of novel chromone derivatives. Bioorg. Chem. 2017, 74, 158–165.
83. Wang, G.; Chen, M.; Qiu, J.; Xie, Z.; Cao, A. Synthesis, in vitro α-glucosidase inhibitory activity and docking studies of novel chromone-isatin derivatives. Bioorg. Med. Chem. Lett. 2018, 28, 113–116.
84. Liu, X.-M.; Tao, T.-T.; Meng, X.-X.; Zhang, W.-W.; Chang, J.; Xu, F. Cloning and Expression Analysis of a Farnesyl Diphosphate Synthase (FPPS) Gene from Chamaemelum nobile. Not. Bot. Horti Agrobot. Cluj-Napoca 2017, 45, 358–364.

85. Li, W.; Liao, G.; Dong, W.-H.; Kong, F.-D.; Wang, P.; Wang, H.; Mei, W.-L.; Dai, H.-F. Sesquiterpenoids from Chinese Agarwood Induced by Artificial Holing. Molecules 2016, 21, 274.
86. Dai, H.F.; Liu, J.; Han, Z.; Zeng, Y.B.; Wang, H.; Mei, W.L. Two new 2-(2-phenylethyl) chromones from Chinese aglewood. J. Asian Nat. Prod. Res. 2010, 12, 134–137.
87. Huo, H.X.; Zhu, Z.X.; Pang, D.R.; Li, Y.T.; Huang, Z.; Shi, S.P.; Zheng, J.; Zhang, Q.; Zhao, Y.F.; Tu, P.F.; et al. Anti-neuroinflammatory sesquiterpenes from Chinese eaglewood. Fitoterapia 2015, 106, 115–121.
88. Yu, M.; Liu, Y.; Feng, J.; Chen, D.; Yang, Y.; Liu, P.; Yu, Z.; Wei, J. Remarkable Phytochemical Characteristics of Chi-Nan Agarwood Induced from New-Found Chi-Nan Germplasm of Aquilaria sinensis Compared with Ordinary Agarwood. Int. J. Analytical Chemistry 2021, 2021, 1–10.
89. Kuang, T.D.; Chen, H.Q.; Kong, F.D.; Cai, C.H.; Yang, L.; Mei, W.L.; Dai, H.F. Three new 2-(2-phenylethyl)chromone derivatives from artificial holing agarwood of Aquilaria sinensis. Phytochem Lett. 2018, 26, 96–100.
90. Zhao, H.; Peng, Q.; Han, Z.; Yang, L.; Wang, Z. Three New Sesquiterpenoids and One New Sesquiterpenoid Derivative from Chinese Eaglewood. Molecules 2016, 21, 281.
91. Tian, H.; Wang, H.; Yang, L.; Gai, C.J.; Dong, W.H.; Li, W.; Mei, W.L.; Dai, H.F. Two new sesquiterpenoids from agarwood originated from Aquilaria sp. J. Asian Nat. Prod. Res. 2020, 22, 626–631.
92. Ueda, J.Y.; Imamura, L.; Tezuka, Y.; Tran, Q.L.; Tsudab, M.; Kadotaa, S. New sesquiterpene from Vietnamese agarwood and its induction effect on brain-derived neurotrophic factor mRNA expression in vitro. Bioorg. Med. Chem. 2006, 14, 3571–3574.
93. Shibata, S.; Sugiyama, T.; Uekusa, Y.; Masui, R.; Narukawa, Y.; Kiuchi, F. Five new 2-(2-phenylethyl)chromone derivatives from agarwood. J Nat Med. 2020, 74, 561–570.
94. Yang, D.L.; Li, W.; Dong, W.H.; Wang, J.; Mei, W.L.; Dai, H.F. Five new 5,11-epoxyguaiane sesquiterpenes in agarwood “qi-nan” from Aquilaria sinensis. Fitoterapia 2016, 112, 191–196.
95. Li, W.; Mei, W.L.; Dong, W.H.; Cai, C.H.; Gai, C.J.; Dai, H.F. Study on chemical constituents of Chinese agarwood “Qi-Nan”. J. Trop. Subtrop. Bot. 2019, 27, 196–202.
96. Nakanishi, T.; Yamagata, E.; Yoneda, K.J. Jinkoh-eremol and jinkohol II, two new sesquiterpene alcohols from agarwood. Chem. Soc. Perkin Trans. 1983, 1, 601–604.
97. Nakanishi, T.; Yamagata, E.; Yoneda, K.; Miura, I. Jinkohol, a prezizane sesquiterpene alcohol from agarwood. Phytochemistry 1981, 20, 1597–1599.
98. Ma, C.T.; Ly, T.L.; Van Le, T.H.; Anh Tran, T.V.; Kwon, S.W.; Park, J.H. Sesquiterpene derivatives from the agarwood of Aquilaria malaccensis and their anti-inflammatory effects on NO production of macrophage RAW 264.7 cells. Phytochemistry 2021, 183, 112630.

99. Chen, D.; Bi, D.; Song, Y.L.; Tu, P.F. Flavonoids from the stems of Aquilaria sinensis. Chin. J. Nat. Med. 2012, 10, 287–291.
100. Ma, C.T.; Cho, E.; Nguyen, H.T.; Wu, B.; Le, T.H.V.; Oh, K.B.; Kwon, S.W.; Nguyen, M.D.; Park, J.H. Malacinones A and B, two novel sesquiterpenoids with 6/6/5 tricyclic ring system from the agarwood of Aquilaria malaccensis. Tetrahedron Lett. 2020, 61, 151355.
101. Yang, L.; Qiao, L.-R.; Zhang, J.-J.; Dai, J.-G.; Guo, S.-X. Two new sesquiterpene derivatives from Chinese eaglewood. J. Asian Nat. Prod. Res. 2012, 14, 1054–1058.
102. Dahham, S.S.; Tabana, Y.M.; Iqbal, M.A.; Ahamed, M.B.K.; Ezzat, M.O.; Majid, A.S.A.; Majid, A.M.S.A. The Anticancer, Antioxidant and Antimicrobial Properties of the Sesquiterpene β-Caryophyllene from the Essential Oil of Aquilaria crassna. Molecules 2015, 20, 11808–11829.
103. Yang, L.; Yang, Y.L.; Dong, W.H.; Li, W.; Wang, P.; Cao, X.; Yuan, J.Z.; Chen, H.Q.; Mei, W.L.; Dai, H.F. New tricyclic prezizaane sesquiterpenoids from agarwood. J. Enzym. Inhib. Med. Chem. 2019, 34, 853–862.
104. Mei, W.L.; Lin, F.; Zuo, W.J.; Wang, H.; Dai, H.F. Cucurbitacins from fruits of Aquilaria sinensis. Chin. J. Nat. Med. 2012, 10, 234–237.
105. Adhikari, S.R.; Pokhrel, K.; Baral, S.D. Economic Value of Agarwood and Its Prospects of Cultivation. Int. J. Appl. Sci. Biotechnol. 2021, 9, 23–31.
106. Swee, L.L.C. Agarwood (Aquilaria malaccensis) in Malaysia, International Expert Workshop on CITES Non-Detriment Findings; Publisher: Cancun, Mexico, 2008.
107. Compton, J.; Ishihara, A. The Use and Trade of Agarwood in Japan; TRAFFIC International: Cambridge, UK, 2004.
108. Antonopoulou, M.; Compton, J.; Perry, L.S.; Al-Mubarak, R. The Trade and Use of Agarwood (Oudh) in the United Arab Emirates; TRAFFIC Southeast Asia: Petaling Jaya, Selangor, Malaysia, 2010.
109. Barden, A.; Anak, N.A.; Mulliken, T.; Song, M. Heart of the Matter: Agarwood Use and Trade and Cites Implementation for Aquilaria Malaccensis; TRAFFIC: Cambridge, UK, 2000.
110. Kiet, L.K. History and ecology of agarwood in Vietnam. In Proceedings of the 1st International Agarwood Conference, Ho Chi Minh City, Vietnam, 10–15 November 2003.
111. Lim, T.W.; Anak, N.A. Wood for the Trees: A Review of the Agarwood (Gaharu) Trade in Malaysia; TRAFFIC Southeast Asia: Petaling Jaya, Selangor, Malaysia, 2010.
112. Persoon, G.A. Growing ‘the Wood of The Gods’: Agarwood production in Southeast Asia. In Smallholder Tree Growing for Rural Development and Environmental Services; Snelder, D.J., Lasco, R.D., Eds.; Springer Science Business Media: Berlin, Germany, 2008; pp. 245–262.

113. Sitepu, I.R.; Santoso, E.; Siran, S.A.; Turjaman, M. Fragrant Wood Gaharu: Whenthe Wild Can No Longer Provide. Forestry Research and Development Agency (FORDA); International Tropical Timber Organization: Yokohama, Japan, 2011.
114. CITES. The Trade and Use of Agarwood in Taiwan, Province of China; TRAFFIC East Asia: Taipei, Taiwan, 2005; Available online: http://cites.org/sites/default/files/common/com/pc/15/X-PC15-07-Inf.pdf (accessed on 18 May 2022).
115. Chakrabarty, K.; Kumar, A.; Menon, V. Trade in Agarwood; TRAFFIC: New Delhi, India, 1994.
116. LaFrankie, J.V. Population dynamics of some tropical trees that yield nontimber forest products. Econ. Bot. 1994, 48, 301–309.
117. Babatunde, O.J. Oud: Arabia's Traditional Scent. 2015. Available online: http://www.masterpiece-ng.com/2015/09/01/oud-arabias traditional-scent/ (accessed on 18 May 2022).
118. Abdin, M.J. The agar wood industry: Yet to utilize in Bangladesh. Int. J. Econ. Manag. Sci. 2014, 3, 163–166.