Mini-review

Synthetic derivatives of aromatic abietane diterpenoids and their biological activities

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ABSTRACT

Naturally occurring aromatic abietane diterpenoids (dehydroabietanes) exhibit a wide range of biological activities. A number of synthetic studies aimed at modifying the abietane skeleton in order to obtain new potential chemotherapeutic agents have been reported. In this study, the biological activities of synthetic derivatives of aromatic abietane diterpenoids are reviewed.

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1. Introduction

Natural products have played a dominant role in the drug discovery efforts for the treatment of human diseases [1]. Abietanes are a family of naturally occurring diterpenoids that have been isolated from a variety of terrestrial plant sources. During the last three decades, many new members of this family of natural products have been isolated and described in several specific reviews on naturally occurring diterpenoids by Professor Hanson [2]. These compounds exhibit a wide variety of interesting biological activities, which has generated significant interest from the medicinal and pharmacological communities. The biological activities of natural abietane acids and their derivatives have been reviewed up to 1992 [3]. In this review, our attention is focused on diterpenoids characterised by tricyclic structures having the abietane (I, C20) carbon framework and an aromatic ring C.

Aromatic abietanes comprised the largest group of components of naturally occurring abietanes. They possess an aromatic ring C and a different degree of oxygenation at several positions. This group of abietanes is exemplified by dehydroabietic acid (2) and ferruginol (3) which were discovered more than seventy years ago [4,5]. Both structures were assigned based on chemical data. Dehydroabietic acid (2) was initially obtained from chemical studies starting from abietic acid (1), later, it was found in resin or extracts of conifers [6]. Ferruginol (3) was firstly isolated in 1939 from the resin of the Miro tree (Podocarpus ferrugineus), endemic to New Zealand [5]. Another typical aromatic abietane is carnosic acid (4), which is found in the popular Lamiaceae herbs, sage (Salvia officinalis) and rosemary (Rosmarinus officinalis) [7]. Dehydroabietylamine (5), an abietane diterpenic amine derived from abietic acid (1), is the main component of disproportionated rosin amine. The diterpenoid skeleton present in these abietanes has been the object of derivatisation in screening for new potential chemotherapeutic agents. In this study, the biological activities of dehydroabietic acid, ferruginol, carnosic acid and dehydroabietylamine derivatives are reviewed.

2. Biological activities of aromatic abietane derivatives

2.1. Dehydroabietic acid derivatives

Over the past few years, a lot of research has been committed to the synthesis of dehydroabietic acid (2, DHA) derivatives. Dehydroabietic acid (2) displays not only antulcer and antimicrobial properties but also antitumour effects. Modifications in rings B and C as well as manipulation of the carboxyl group at C-18 of DHA (2) have been studied in order to enhance its properties. In one of the early studies aimed at searching for new antulcer agents with a broad cytoprotective effect, Wada et al. prepared more than
seventy derivatives of DHA (2), introducing a hydrophilic residue (amino, carbamoyl, carbamate, ureide, sulfonil, or sulfamoyl) onto the lipophilic dehydroabietane skeleton [8]. The antiserumetic and antipepsin activities were evaluated as a preliminary evaluation of antiulcer activity. The results obtained showed that DHA (2) has a moderate antiserumetic action (22% inhibition of secretion at an intraperitoneally dose of 30 mg/kg, rats) and had no antipepsin activity. Among the tested compounds, the salts of 12-sulfodehydroabietic acid (6a–b) (Fig. 2) were found to exhibit remarkably high antipepsin activity (92–96% inhibition at 100 mg/kg) without aldosterone-like activity shown by other antiulcer agents. Further research on the molecule 6a [12-sulfodehydroabietic acid monosodium salt] has led to the development of the drug ecaber® (ecabet sodium) for the treatment of gastric ulcer disease. The gastroprotective and cytotoxic effect of a series of DHA (2) derivatives at C-18 has been reported [9]. In this study, DHA (2) presented a dose-related gastroprotective effect on HCl/EtOH-induced gastric lesions in mice (59% inhibition at 100 mg/kg). The aromatic amide derivatives 7a–g (Fig. 2) showed a strong gastroprotective activity (67–85% inhibition of gastric lesions) with low cytotoxicity (IC50 > 1000 μM) for both fibroblasts (MRC-5) and human epithelial gastric cell line (AGS).

The antimicrobial activity of resin acid derivatives has been reviewed up to 2006, including some DHA (2) derivatives [10]. For example, C-13 desisopropylated compounds 8 and 9 (Fig. 3) were the most active inhibiting the growth of several filamentous fungi (Actinomucor harizi, Cladosporium cucumerinum, Mucor racemosus, Rhizopus arrhizus, Rhizopus stolonifer, and Syncephalastrum racemosum) and also the Gram-positive bacterium Staphylococcus aureus [11]. Both compounds did not inhibit the growth of Gram-negative bacteria, Escherichia coli and Klebsiella pneumoniae. However, in combination, those two compounds (8 and 9) inhibited the growth of those organisms suggesting a synergistic effect. The presence of an aldehyde group, compounds 10a and 10b (Fig. 3), seemed to be important for the antiyeast activity against Candida albicans, Candida krusei and Candida parapsilosis [12]. More recently, González et al. demonstrated that DHA (2) (MIC = 39.7 μg/mL against Aspergillus terreus) and dehydroabietane 11a (Fig. 3) (MIC = 50 and 63 μg/mL against Aspergillus fumigates and Aspergillus niger, respectively) possess anti-Aspergillus activity [13]. These authors also described anti-Aspergillus activity for the phenol 11b (Fig. 3) (MIC = 25, 25 and 50 μg/mL against A. fumigates, A. terreus and A. niger, respectively) [14]. A series of DHA (2) derivatives bearing 1,4-triazolo-thiazolidinone moieties, compounds 12a–g (Fig. 3), have been synthesised and tested at 50 μg/mL for antifungal activity against Fusarium oxysporum, Alternaria solani, Physalospora piricola, Cercospora arachidicola and Fusarium graminearum [15]. With the exception of 12c, all compounds were most effective against F. graminearum, being compound 12d the most potent with inhibition ratio of 70.9%. Compound 12c showed the greatest inhibition ratio of 51.9% against F. oxysporum, and compound 12e displayed the greatest inhibition ratio of 56.8% against P. piricola.

Other antimicrobial studies include the synthesis of some thioureas, compounds 13a–k (Fig. 4), and the corresponding 1,2,4-triazolo-aniline derivatives 14a–f (Fig. 4), which were tested against Bacillus subtilis and E. coli [16]. Compounds 13j, 13e, 13f and 14b possess antibacterial activity against B. subtilis at a test concentration (for 13j: 50 mg/mL; for 13e, 13f, 14b: 100 mg/mL) while compounds 13b, 13h, 13i and 14e possess antibacterial activity against E. coli at a test concentration of 100 mg/mL.

A series of novel dibenzo-carbazole derivatives of DHA (2), compounds 15a–m (Fig. 4), were synthesised and tested against four bacteria (B. subtilis, S. aureus, E. coli, and Pseudomonas fluorescens) and three fungi (Trichophyton rubrum, C. albicans and A. niger) [17]. Among the compounds tested, 15d, 15e, 15f and 15m exhibited pronounced antibacterial activities and 15e and 15m also showed moderate antifungal activities. Particularly, 15d exhibited stronger antibacterial activity against B. subtilis (MIC = 1.9 μg/mL) comparable to positive control (amikacin, MIC = 0.9 μg/mL). Later, on, the same authors reported the synthesis and antimicrobial evaluation of N-substituted dibenzo-carbazole derivatives of DHA (2), compounds 16a–s (Fig. 4) [18]. Some of the synthesised compounds displayed pronounced antimicrobial activity against four bacteria (B. subtilis, S. aureus, E. coli, and P. fluorescens) with low MIC values ranging from 0.9 to 15.6 μg/mL. Among them, compounds 16j and 16r exhibited potent inhibitory activity comparable to reference drug amikacin. These authors have also described the synthesis and antibacterial evaluation of new N-acylhydrazone derivatives, compounds 17a–q (Fig. 4), from DHA (2) [19]. The compounds were evaluated against four microbial strains (B.
agents were comparable to that of acyclovir (IC50 ... Human embryonic lung (CMV) replication at a concentration ca. 5- to 10-fold lower than the positive control (amikacin, MIC ≤ 0.9 μg/mL). Compounds 17i, 17n and 17p also showed strong inhibitions (3.9–7.8 μg/mL) against the Gram-negative strains E. coli and P. fluorescens.

The antiviral activity of DHA (2) derivatives has also been studied. For example, Fonseca et al. described the synthesis of novel heterocycles (Fig. 5), such as benzimidazoles (18a–g), quinoxalines (19a–c), and indoles 20 and 21 as potential antiviral agents [20]. Biological evaluation showed that compounds 18b, 18e, 19c, and 21 inhibited both varicella-zoster virus (VZV) and cytomegalovirus (CMV) replication at a concentration ca. 5- to 10-fold lower than the cytotoxic concentration, when tested in human embryonic lung cells. The potencies of 18a, 18b, 18d, 18e, 19c, 20 and 21 as anti-VZV agents were comparable to that of acyclovir (IC50 = 0.3–3.0 μg/mL), while the potencies of 18a, 18b, 18e, 19c, 20 and 21 as anti-CMV agents were comparable to that of ganciclovir (IC50 = 0.9–1.5 μg/mL). However, all these derivatives were not active against herpes simplex virus (HSV-1 and HSV-2), vaccinia virus, vesicular stomatitis virus, Coxackie virus B4, respiratory syncytial virus, and human immunodeficiency virus at a concentration of 400 μg/mL. Two different studies confirmed anti-herpetic activity for DHA (2) derivatives. Firstly, Tagat et al. reported that A-ring hydroxylated compounds 22a and 22b (Fig. 5) show HSV-2 inhibitory activity and concluded that they interfere with an early event in viral replication [21]. And secondly, Gonzalez et al. described that dehydroabietinol acetate 23 (Fig. 5) showed significant anti-herpetic activity of broad spectrum [13, 22].

DHA (2) has exhibited strong inhibitory effects on Epstein–Barr virus early antigen (EBV-EA) activation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) and was selected to examine effects on in vivo two-stage mouse skin carcinogenesis. It exhibited high activity in this antitumour-promoting test [23]. Two oxidation products of methyl abietate, compounds 24a and 24b (Fig. 6), have displayed weak cytotoxicity against KB cells (IC50 = 4.5 and 5.8 μg/mL, respectively) [24]. Rao et al. reported a cytotoxicity study on liver cancer cells (SMMC7721) of a number of N,N'-substituted ureas (e.g. 25a–d) (Fig. 6) synthesised from DHA (2) [25]. Their IC50 values were between 8.8 and 14.2 μM. The change of N'-substituted groups resulted little difference to the cytotoxicity activities of ureas, which indicated that the cytotoxicity of this kind of ureas depend strongly on the tricyclic hydrophenanthrene structure. Later on, these authors described the synthesis and antitumour activities of several acylthioureas (e.g. 26) (Fig. 6) on liver cancer cells (SMMC7721) and lung cancer cells (A549) [26]. Compound 26 exhibited higher inhibition ratio against A549 than SMMC7721 (82.89% and 61.72%, respectively). Its IC50 was 6.44 μM for A549 and 6.84 μM for SMMC7721. Recently, Zhang et al. continued this research on thioureas and studied novel α-aminophosphonates dehydroabietic acid derivatives (e.g. 27a–c) (Fig. 6) against several human cancer cell lines, including NCI-H460 (lung), A549 (lung), HepG2 (liver) and SKOV3 (ovarian) [27]. Compound 27a exhibited the best antitumour activity on NCI-H460 with IC50 of 3.33 μM and demonstrated better cytotoxic inhibition than 5-fluorouracil (5-FU) in all tested cell lines. Its apoptosis-inducing activity on NCI-H460 cells was studied and the results revealed that this compound showed clear cell apoptosis inducing effects. Also, C7-functionalised derivative 27c exhibited high level of antitumour activities against the tested cancer cell lines and demonstrated to be more potent compared with the commercial anticancer drug 5-FU. This compound induced cell apoptosis in A549 cells. The cytotoxic activities of several amino acid-conjugate derivatives of DHA (2), compounds 28a–h (Fig. 6), against four human cancer cell lines (HL60, leukaemia, A549, lung, AZ521, stomach) and (SK-BR-3, breast) have been reported [28]. All compounds showed cytotoxicity against HL60 cells with IC50 values in the range of 2.3–37.3 μM. In addition, most of the derivatives exhibited moderate cytotoxicity against the other cancer cell lines. Among the derivatives, L-tyrosine derivative 28g exhibited potent activities against the four cancer cell lines with IC50 values of 2.3 (HL60), 7.1 (A549), 3.9 (AZ521), and...
8.1 μM (SK-BR-3), respectively. Furthermore, all derivatives were shown to possess high selective cytotoxic activities for leukaemia cells, since they exhibited only weak cytotoxicity against normal lymphocyte cell line RPMI1788. In connection with this research, Zhang et al. described the synthesis and antitumour activities of novel dipeptide derivatives, compounds 29a–e (Fig. 6), derived from DHA (2) [29]. The antitumour activity screening indicated that many compounds showed moderate to high levels of inhibition activities against NCI-H460 (lung), HepG2 (liver), SKOV3 (ovarian), BEL-7404 (liver), HeLa (cervical) and HCT-116 (colon) cancer cell lines and that some displayed more potent inhibitory activities than commercial anticancer drug 5-FU. The mechanism of representative compound 29b was studied which demonstrated that it induced apoptosis in HeLa cells through a mitochondrial pathway. Recently, Pertino et al. reported on the synthesis and anti-proliferative activity of some novel triazole derivatives of DHA (2), compounds 30a–d and 31a–e (Fig. 6) [30]. The best results were obtained for compound 31a which presented an IC50 value of 6.1 μM in the SK-MES-1 cell line derived from metastatic site. Under the same experimental conditions, the IC50 value of etoposide was 1.83 μM.

The redox properties of several diarylamines (e.g. 32a–d) (Fig. 7) derived from DHA (2) have been investigated by cyclic voltammetry, and their free radical scavenging activity was tested by reduction of the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical [31]. Compounds 32a, 32c and 32d with lower oxidation potential proved to be as active as isopropylidiphenylamine (IPPD) and superior to tert-butylhydroxytoluene (BHT). In order to probe the antioxidant effect of a series of methyl 12-imino-13-nitro dehydroisopropylabietate derivatives (33a–d) (Fig. 7), the metal ion binding abilities on Cu2+ and Fe2+ of these derivatives were studied using fluorescence quenching method [32]. The results indicated that each compound showed obvious chelation activity with the binding constants (Kst) of the 102 L mol−1 order of magnitude, which implied its potential pharmacology application as antioxidant by the inhibition of Fenton reaction through chelation with Cu2+ and Fe2+. Compound 33b has the strongest chelation activity with Cu2+, while 33d has the strongest chelation activity with Fe2+, respectively.

The biological activity of a series of amino derivatives of DHA (2) (e.g. 34) (Fig. 7) has been studied. Compound 34 produces a calming effect, anxiolytic activity, and antipyretic action comparable with that of the reference drug analgin in mice [33].

In order to explore novel scaffolds for large-conductance calcium-activated K+ channel openers (BK channels), Ohwada et al. selected the aromatic ring of DHA (2) for structural modification. Well-characterised BK channel openers could be used to treat acute stroke, epilepsy, and bladder overactivity. There is some evidence for the utility of BK channel openers in the treatment of asthma, hypertension, gastric hypermotility and psychoses. Thus, this research group has investigated a number of derivatives, compounds 35–38 (Fig. 8), as BK channel openers. For example, the early studies found that 12,14-dichlorodehydroabietic acid (35) showed a remarkable increase of the BK channel-opening activities (Fig. 7), the metal ion binding effect with Cu2+ and Fe2+ of these derivatives was studied. Compound 33b has the strongest chelation activity with Cu2+, while 33d has the strongest chelation activity with Fe2+, respectively.
derivatives have been patented as antibacterials and anticancer agents [42–43]. One of the early studies on antimicrobial activity of DHAA (5) found that several peptoid derivatives (e.g. 41–42) (Fig. 9) were also active in the range 3–12 μg/mL against a panel of Gram-positive and Gram-negative bacteria, which included isolates which were resistant to known antibiotics [44]. The antimicrobial activity of these compounds was generally slightly more potent against Gram-positive than Gram-negative isolates. The activity against S. aureus was rapid, bactericidal, and independent of protein synthesis. Compound 42a protected S. aureus-infected mice in a simple infection model. The antibacterial activity of DHAA (5) against B. subtilis and S. aureus as well as two fungi strains (Poria placenta and Rhizopus oryzae) has also been reported [45]. DHAA (5) showed strong activity against the two bacteria, and presented fairly similar antibiotic activity against fungus of R. oryzae but little activity against fungus of P. placenta. Several quaternary ammonium salts (43–44) (Fig. 9) obtained from DHAA (5) displayed antibacterial activity against S. aureus and E. coli with MIC values in the range of 7.81–31.25 μg/mL for S. aureus, and 250–500 μg/mL for E. coli [46]. It was also found that the ammonium salts with N,N-dimethyl groups had stronger activity than those with N,N-diethyloxy groups. Other derivatives of DHAA (5), such as Schiff base derivatives (45a–h) (Fig. 9), obtained by reaction of the amino group have shown antibacterial activity against S. aureus, B. subtilis and E. coli [47]. All the compounds exhibited bactericidal activity. Compound 45c derived from Cl-substituted benzaldehyde was the most active towards B. subtilis, and compound 45d derived from fluorinated benzaldehyde, toward S. aureus. The most active agent toward E. coli was compound 45a derived from unsubstituted benzaldehyde. The bactericidal activity of ring B derivatives of DHAA (5) such as 12-nitro-dehydroabietylamine (46a) and 12,14-dinitro-dehydroabietylamine (46b) has also been reported [48]. Both compounds had strong bactericidal activity against E. coli, S. aureus and P. fluorescens.

Recently, DHAA (5) has been studied for treating melanoma showing a novel mechanism of action. It was 4.5-fold more effective at inhibiting cultured melanoma cell survival than normal cells, with average IC50 values of 2 and 9.3 μM, respectively [49]. It also inhibited the growth of preexisting xenografted melanoma tumours by an average of 60% without affecting animal body weight or blood markers of major organ function. The potent biological profile of DHAA (5) has spurred the synthesis of a number of derivatives (47–56) (Fig. 10) for studying their antitumour properties. For example, a series of novel x-aminophosphonate derivatives, compounds 47a–j (Fig. 10), have been synthesised by Rao et al. and evaluated for their antitumour activities against SMMC7721 liver cancer cells [50]. Compounds 47d and 47f exhibited higher activities even at very low concentrations, and the inhibition ratios reached 75% and 79% at 0.1 μM, respectively. The inhibition ratio of compound 47i reached 99% after 72 h incubation. The derivatives with a fluorine atom and a nitro group fused to the benzene ring exhibited higher activities. The same authors have reported that dehydroabietylamine derivative 48a (TBIDOM) (Fig. 10) exhibited significant antiproliferative effects by induction of apoptosis in SMMC7721 liver cancer cells. Its mechanism may be related to the decrease in the expression of anti-apoptotic protein, Bcl-2, accompanied by a drop in the mitochondrial membrane potential and the activation of caspase-3, that led to apoptotic body formation and finally apoptosis [51]. Similarly, dehydroabietylamine-fluorobenzaldehyde derivative 48b (Fig. 10) displayed a significant inhibitory effect on the growth of SMMC7721 cells in a dose- and time-dependent manner (IC50 = 44.5 μM) [52]. Also, compound 48b could significantly reduce tumour weight in the H22 solid tumour mouse model in vivo. A series of Schiff bases, compounds 49a–e (Fig. 10), derived from 12-amino-N-acetyldehydroabietylamine

Fig. 8. BK channel openers based on DHA derivatives 35–38 and anti-inflammatory derivatives 39 and 40.

Fig. 9. Antimicrobial DHAA derivatives 41–46.
have been synthesised and evaluated for their antitumour activities on Hey-1B ovarian cancer cell line [53]. The IC₅₀ values were in the range of 15–20 µg/mL. The urea derivative 50 (Fig. 10) showed a significant dose-dependent and time-dependent inhibition of growth of human hepatoma HepG2 cells (IC₅₀ = 3.81 µM) [54]. It possibly has its effect by inhibition of glycolysis and glycolysis-dependent ATP depletion. The isothiocyanate derivative 51 (Fig. 10) at concentrations ca. 1 µM displayed dose-dependent and selective cytotoxicity to endometrial cancer cells in comparison to other cancer cell lines [55]. Lin et al. have prepared several benzamide derivatives, compounds 52a–c and 53a–c (Fig. 10), with a carbonyl group at C-7 on ring B or a nitro group at C-12 on ring C and evaluated the influence of these groups on the cytotoxicity against PC-3 (prostate) and Hey-1B (ovarian) cancer cell lines [56]. The results showed that the presence of either a carbonyl or a nitro group increased the cytotoxic activity. Among these compounds, 52a and 53a–c showed good cytotoxicities against PC-3 cancer cells (IC₅₀ = 5.7–8.2 µg/mL) and Hey-1B cancer cells (IC₅₀ = 11.3–16.0 µg/mL). These researchers also carried out a screening of 73 dehydroabietylamine derivatives as potential candidate inhibitors of the growth of liver cancer cells. In this study, N-benzoyl-12-nitrodehydroabietylamine-7-one (54) (Fig. 10) demonstrated to have significant growth inhibitory activity in the human liver cancer cell line, HepG2 (IC₅₀ = 67.86 µg/mL) [57]. Further research confirmed that this compound effectively induced apoptosis and inhibited HepG2 cell proliferation by blocking DNA synthesis. However, another study of this research group showed that one or two nitro groups in ring C of DHAA (5) together with aromatic imines gave highly cytotoxic compounds to normal human hepatocyte (LO2) cells [58]. Recently, Rao et al. screened a series of imines, amides and ureas with a dehydroabietyl skeleton for their antitumour activities against SMMC7721 (liver), A549 (lung), C6 (glioma) and MCF-7 (breast) cancer cell lines [59]. Imines 55a–d (Fig. 10) possess noticeable antitumour activity against SMMC7721, A549, C6 and MCF-7 cancer cells, with lowest IC₅₀ values of 6.65, 0.75, 0.81, and 10.65 µM, respectively. The antitumour activity of DHAA (5) against two bladder cancer cell lines (EJ and 5637), one prostate cancer cell line (PC-3), one cervical cancer cell line (HeLa) and one human T-cell leukaemia cancer cell line (Jurkat) was improved with the attachment of quinidine via thiourea bond [60]. Thus, compound 56 (Fig. 10) exhibited broad spectrum of activity (IC₅₀ = 2.07–3.21 µM) against the tested cancer cell lines with little toxicity to normal cells, and induced apoptosis mainly through mitochondrial-dependent pathway.

But the biological properties of DHAA (5) derivatives go beyond antimicrobial and antitumour activities. For example, the anti-inflammatory activity of four derivatives of DHAA (5), compounds 57–60 (Fig. 11), has also been described. These compounds were found to be active as topical inflammation inhibitors as demonstrated in the tetradecanoylphorbol acetate induced ear oedema assay [61]. The derivative N-benzoyl-dehydroabietylamine-7-one (61) (Fig. 11) has been found to possess certain androgen receptor binding activity with IC₅₀ value of 83.8 µM [62]. And the imine derivative 62 (Fig. 11) displayed tyrosine kinase inhibitory activity (FGFR1, IC₅₀ = 1.20 µM) [63]. The antioxidative activity of derivative 63 (Fig. 11), which resulted from merging gallic acid and DHAA (5) through an amide bond, has also been reported [64]. Compound 63...
was tested for the ability on scavenging superoxide anion radical and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. The results indicate that the inhibitory rate of superoxide anion radical by 63 was 38.18% which is twice as much as that of l-ascorbic acid (18.35%) and its capacity on scavenging DPPH radical (IC50 = 2 mg/L) is much better than l-ascorbic acid (IC50 = 236 mg/L).

In addition, DHAA (5) is a known inhibitor of pyruvate dehydrogenase kinase (PDK) which could have utility as a therapy for diabetes, ischaemia, lactic acidosis and cardiac insufficiency [65].

2.3. Ferruginol derivatives

Ferruginol (3) (Fig. 1) is an abietane diterpenoid that occurs in plants belonging to the Podocarpaceae, Cuscutaceae, Lamiaceae and Verbenaceae families among others. This abietane has attracted much attention since it has exhibited promising bioactivities, such as antifungal and antimicrobial [66], cardioactive [67], antileishmanial and nematicidal [69]. In addition, ferruginol (3) has recently shown antitumour activity against prostate cancer [70], cytotoxicity against human pancreatic tumour cell lines [71], as well as anti-inflammatory activity [72]. This diterpene has also shown a strong protective effect in animal gastric ulcer models [73]. However, it has demonstrated high oxidative [68], antileishmanial and nematicidal [69]. In addition, ferruginol (3) has recently shown antitumour activity against prostate cancer [70], cytotoxicity against human pancreatic tumour cell lines [71], as well as anti-inflammatory activity [72]. This diterpene has also shown a strong protective effect in animal gastric ulcer models [73]. However, it has demonstrated high oxidative [68], antileishmanial and nematicidal [69].

Compound 67a–d (Fig. 13) from abietic acid and evaluated several biological activities, including antifungal, antitumour, antiviral and inhibition of nitric oxide (NO) production [77]. Compounds 68a and 68d exhibited potent antifungal activity against dermatophytes Microsporum canis, Trichophyton mentagrophytes and Epidermophyton floccosum, being more potent (MIC = 13.1–210.0 μM) than the control drug fluconazole (MIC = 52.2–208.9 μM). Catechols 68a–d were potent inhibitors of NO production (IC50 = 5.2–18.5 μM) and also displayed moderate antitumour activity. Compound 68a was found to have antiherpetic activity and moderate anti-HIV activity (EC50 = 275 μM). Later on, this research group demonstrated the potential application of compound 68a as antioxidant [78].

Thus, the best gastroprotective effect was elicited by ferruginyl nicotinate (65e), reducing the lesion index by 71%, while the derivatives ferruginyl palmitate (65a), ferruginyl oleate (65b), ferruginyl 3,5-dinitrobenzoate (65c), ferruginyl 3-methylbenzofuran-2-carbonyl ester (65d), ferruginyl indoleacetate (65f) and ferruginyl indolebutyrate (65g) reduced the lesions by 50–66%. The most promising compounds were 65c, 65e and 65f, presenting a gastroprotective effect higher or similar to that of ferruginol (3) but with a high selectivity towards the tumour AGS cells. Among these three products, the most selective towards AGS cells was 65f, followed by 65e, and 65c (IC50 values of 12, 22, and 29 μM, respectively). The cytotoxicity of the above cited compounds towards fibroblasts was >1000 μM.

Fig. 12. Antiulcer ferruginol derivatives 64 and 65.

Fig. 13. Bioactive ferruginol derivatives 66–73.
Tada et al. developed a synthetic route to (+)-ferruginol (3) and the corresponding enantiomer (−)-ferruginol. Using this methodology, this research group prepared various oxidised abietanes, including catechols 69a and 69b (Fig. 13), 6-oxoferruginol (70a) and 6β-hydroxyferruginol (70b) (Fig. 13) and evaluated their antimicrobial activity against methicillin-resistant S. aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) [79]. Compounds 69–70 showed potent activity with MIC values of 4–8 μg/mL against MRSA and 4–16 μg/mL against VRE. Non-natural (−)-ferruginol showed stronger activity than natural (+)-ferruginol (3).

Recently, Sánchez-Moreno et al. reported on the antileishmanial activity (Leishmania infantum and Leishmania braziliensis) of several phenol abietanes related to ferruginol (3), compounds 71–73 (Fig. 13) [80]. These compounds were more active (IC50 = 14.0–31.6 μM) and less toxic than the reference drug glucantime.

2.4. Carnosol and carnosic acid derivatives

Carnosol (CS, 74) (Fig. 14) and carnosic acid (CA, 4) (Fig. 1) are found in the popular Lamiaceae herbs, sage (Salvia officinalis) and rosemary (Rosmarinus officinalis). Both possess an o-diphenol structure (catechol) which undergoes oxidation easily and provides potent antioxidant activity. The early studies on biological activity of derivatives of these abietanes considered particularly the antioxidant activity. For example, Nakatani et al. reported on the antioxidant activity of compounds 74–77 (Fig. 14) derived from carnosol (74) and rosmarinic acid (76a), a related catechol, respectively [81]. In general, when the phenol is fully substituted there is a decrease in activity while mono-substituted derivatives were as strong antioxidants as the parent compounds. Preparative-scale incubations of CA (4) with Nocardia sp. led to the isolation of derivatives 77 and 78 (Fig. 14), which were evaluated for antioxidant activity using the DPPH free-radical scavenging assay [82]. Both compounds showed activities similar to that of tocopherol and CA (4).

Takeya et al. prepared several semisynthetic derivatives from CA (4), including compounds 79a–b (Fig. 14), and examined the cytotoxic activity using P388 murine leukaemia cells [83]. Substitution of the phenol groups decreased the cytotoxicity, compound 79b (IC50 = 5.9 μg/mL), but the free hydroxyl groups along with the ester group at C-20, compound 79a (IC50 = 0.6 μg/mL), gave more potent activity than CA (4) (IC50 = 1.2 μg/mL). In another study, compound 79b also showed cytotoxicity against breast (MCF-7) cancer cell line (IC50 = 69 μM) as well as activity against Mycobacterium tuberculosis (MIC = 28 μM), being more potent than carnosol (74) [84].

The gastroprotective activity of carnosic acid (4) derivatives has also been reported. For example, Schmeda-Hirschmann et al. described the synthesis and evaluation of a series of γ-lactone derivatives (e.g. 80a–d) (Fig. 14) of carnosic acid (4) in the HCl/ethanol-induced gastric lesion model in mice, as well as cytotoxicity in human gastric adenocarcinoma (AGS) and human lung fibroblasts (MRC-5) cells [85]. Compounds 80a–d showed the highest gastroprotective effect (65–82% lesion reduction), however, compound 80a was more cytotoxic (IC50 = 130 μM for MRC-5 and 103 μM for AGS) than compounds 80c and 80d, which presented IC50 values of >1000 μM against MRC-5 cells and >1000 μM and 822 μM toward AGS cells, respectively. Later on, this research group reported on the gastroprotective effect of further derivatives of carnosic acid (4), compounds 81–83 (Fig. 14). At 10 mg/kg, compounds 81–83 were more effective preventing gastric lesions (73–78% lesion reduction) than the reference drug lansoprazole at the same dose (64% lesion reduction). These compounds showed the best gastroprotective effect combines with the lowest cytotoxicity [86]. Their mechanism of action has also been studied, which includes protection against cell damage induced by sodium taurocholate, increase in glutathione content, stimulation of prostaglandin E2 synthesis and cell proliferation [87].

3. Conclusion

A number of derivatives of natural aromatic abietanes have been synthesised and studied for biological properties. The encouraging findings warrant further interesting studies in this area of research, which could provide with novel chemotherapeutics and chemical probes.

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References
