CHAPTER 2

Review of Literature

Terpenoids, also called isoprenoids, are substances that are made up from isoprene (2-methylbuta- 1, 3-diene) units. Most of the terpenoids are plant origin and more than 40,000 individual compounds have been accounted. In plants, some terpenoids are involved in cellular function and maintenance as primary metabolites. However, thousands of terpenoids produced by plants have been characterized as secondary metabolites and they show significant pharmacological applications such as anti-viral, anti-bacterial, anti-malarial, anti-inflammatory, inhibition of cholesterol synthesis and anti-cancer activities [1]. So many researchers have paid attentions on naturally obtained terpenoids or their synthetic modifications and developed quantitative structure activity relationships (QSARs) of a number of terpenoids with different biological activities in order to predict the activity of the compounds that have not yet been synthesized or experimentally tested.

This review work has been briefly divided into two subgroups which are as follows:

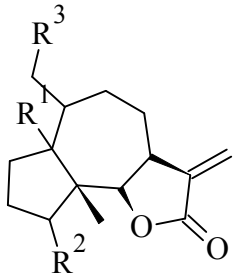
2.1. Terpenoids with different biological activity

2.2. Quantitative structure-activity relationships of bioactive terpenoids

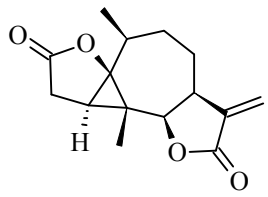
2.1. Terpenoids with different biological activity

Terpenoids are the most abundant and diverse class of natural products. Many biological activities of terpenoids have made them a widely used resource for traditional and modern human utilization. The sesquiterpene lactones are known for their wide variety of biological activities. Some medicinal plants containing sesquiterpene lactones show anti-inflammatory

properties. Recio et al. reported the in vivo anti-inflammatory activities of seven pseudoguaianolide type of sesquiterpene lactones: 4-α-Oacetyl- pseudoguaian-6β-olide (1), hymenin (2), ambrosanolide (3), tetraneurin (4), parthenin (5), hysterin (6) and confertdiolide (7) isolated from several species of Parthenium where confertdiolide (7) was the most active compound [2-6].

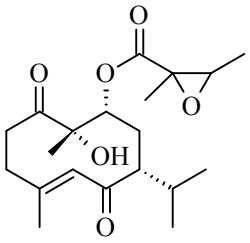


(1): R^1=α-H, R^2=α-OAc, R^3=H; (2): R^1=α-OH, R^2=O, R^3=H; (3): R^1=α-OH, R^2=β-OAc, R^3=H; (4): R^1=α-OH, R^2=O, R^3=OAc; (5): R^1=β-OH, R^2=O, R^3=H; (6): R^1=α-H, R^2=α-OAc, R^3=OH



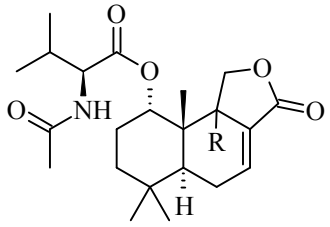
(7)

Ishibashi et al. isolated two new sesquiterpenoid esters with nine known flavonoids from *Blumea balsamifera*, a tropical Compositae plant. Compound (8) proved to be weakly cytotoxic against Jurkat human T-cell leukemia cells [7].



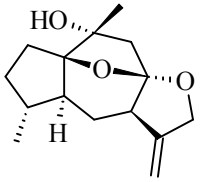
(8)

Stierle et al. isolated two new drimane sesquiterpene lactones and one new tricarboxylic acid derivative from the Berkeley Pit extremophilic fungus *Penicillium solitum*. The structures of the new compounds were elucidated by spectroscopic analyses and it was found that berkedrimanes A (9) and berkedrimanes B (10) inhibited the signal transduction enzymes caspase-1 and caspase-3 and mitigated the production of interleukin 1-β in the induced THP-1 (pro-monocytic leukemia cell line) assay [8].



(9): R=H; (10): R=OH

Zhao et al. isolated two new sesquiterpenoids with guaiane skeletons holosericin A (11) and holosericin B (12) from the medicinal plant *Daphne holosericea* (Diels) Hamawa (Thymelaeceae). Both the compounds were evaluated for inhibitory activities against acetylcholinesterase and compound (12) exhibited a moderate activity with 31% inhibition [9].



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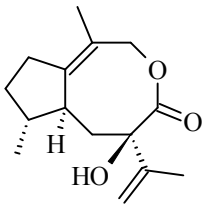
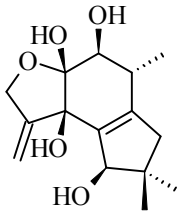


(12)

Liu et al. have isolated some sesquiterpenoids, clitocybulol derivatives from the solid culture of the edible fungus *Pleurotus cystidiosus*. Compounds (13) and (14) exhibited moderate inhibitory activity against protein tyrosine phosphatase-1B (PTP1B) with IC_{50} values of 49.5 μM and 38.1μM respectively [10].



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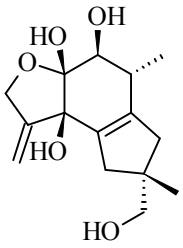
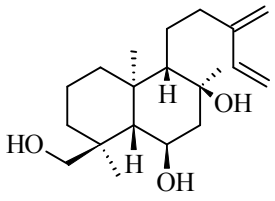


(14)

A large number of diterpenoids have been reported for several biological actions including antibacterial, antifungal, antiinflammatory, antileishmanial, antialgal, cytotoxic and antitumour activities [11-15]. Andalusol (15) and abietic acid (16) exhibited anti-inflammatory activities in vivo and in vitro models of inflammation [16, 17].



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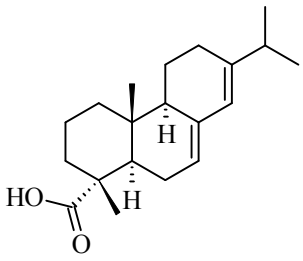
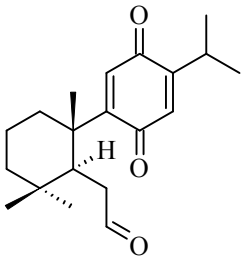


(16)

Zhang et al. isolated a new 7,8-seco-abietane diterpene derivative, 7,8-seco-para-ferruginone (17), and two new 4,5-seco-5,10-friedo-abietane diterpenoids, 4-hydroxysaprorthoquinone (18) and 3-keto-4- hydroxysaprorthoquinone (19) together with two new compounds from the roots of *Salvia prionitis*. Compound 17 showed antimicrobial activities against Staphylococcus aureus and Micrococcus luteus. Compound 18 exhibited significant inhibitions against topoisomerase I. Compound 19 displayed cytotoxic activities against HL-60 human leukemia and the SGC-7901 and MKN-28 stomach cancer cell lines [18].



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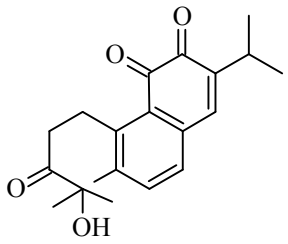

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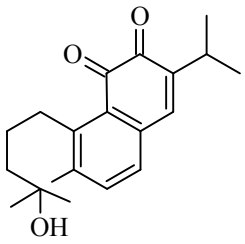
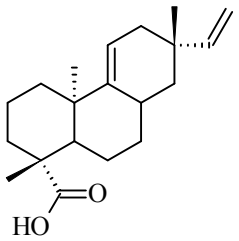


(19)

Ahn et al. isolated eight diterpenoids from CH_2Cl_2-soluble extract of the roots of *Acanthopanax koreanum* (Araliaceae) and were evaluated for their inhibitory effect on protein tyrosine phosphatase 1B (PTP1B) which has been proposed as a therapeutic target for the treatment of type 2 diabetes and obesity. A kaurane-type diterpene, 16αH,17-isovaleryloxy-*ent*-kauran-19-oic

acid (20), inhibited PTP1B in a non-competitive manner where as acanthoic acid (21) and *ent*-kaur-16-en-19-oic acid (22) inhibited PTP1B in dose-dependent manners [19].



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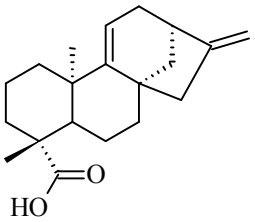

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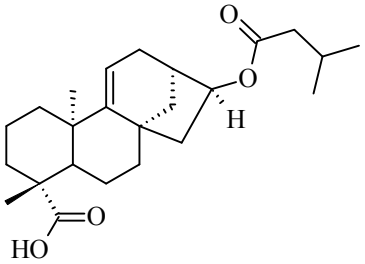
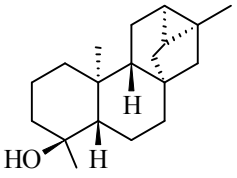


(22)

Litaudon et al. isolated a new diterpenoid ent-trachyloban-4β-ol (23), and five known ent-trachylobane or ent-atisane compounds from *Xylopia caudata*. All the compounds exhibited cytotoxicity against KB and HCT-116 cell lines and only ent-trachyloban-18-oic acid (24) exhibited weak binding activity to antiapoptotic protein Bcl-xL [20].



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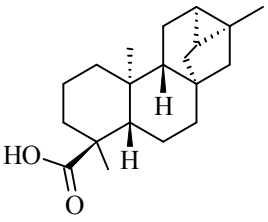
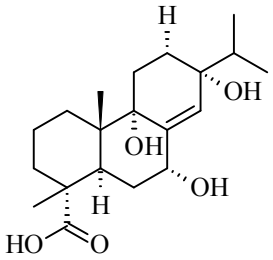


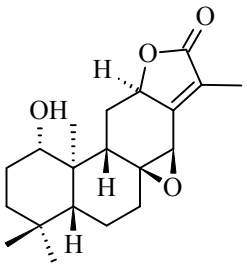
(24)

Guo et al. extracted ten new abietane diterpenoids, aquilarabietic acids A–J, and a new podocarpane diterpenoid, aquilarabietic acid K from the petroleum ether and ethanol extracts of Chinese eaglewood. Aquilarabietic acids A (25) exhibited remarkable antidepressant activity in vitro by inhibiting norepinephrine reuptake in rat brain synaptosomes by 81.4% [21].



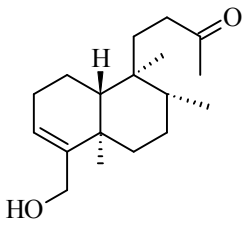
(25)

Yue et al. reported that some isolated diterpenoids, named eurifoloids A–R, from *Euphorbia neriifolia* exhibited anti-HIV activities. It was stated that eurifoloids F (26) showed significant anti-HIV activities with EC_{50} values of 7.40 ± 0.94 μM [22].



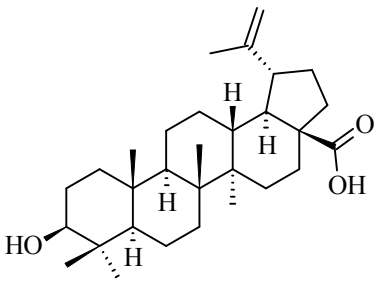
(26)

Luo et al. isolated five new iridoid glucoside derivatives, three new diterpenoids and 11 known compounds from the aqueous EtOH extract of *Caryopteris glutinosa*. Cell-based estrogen biosynthesis assays indicated that caryopterisoid B (27), a diterpenoid, promote the biosynthesis of estrogen E2, with EC_{50} values 8.0 μM, in human ovarian granulosa-like KGN cells via upregulating the expression of aromatase [23].



(27)

Triterpenoids often exhibit a variety of biological activities such as anti-HIV, anti-inflammatory, ichthyotoxic, anti-tumour-promotin and antimycobacterial activities [24-30]. Lee et al. isolated betulinic acid (28) and platanic acid (29) from the leaves of *Syzigium claviflorum*. These compounds were found to be inhibitors of HIV replication in H9 lymphocyte cells [31].



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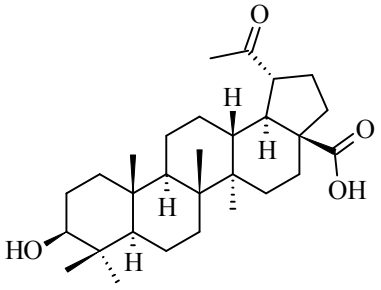
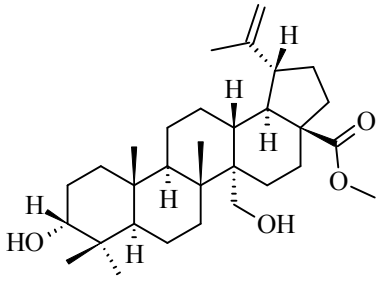


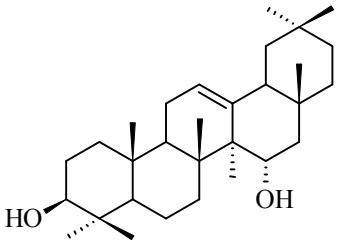
(29)

Nomura et al. isolated three new triterpenoids, 3α, 27-dihydroxylup-20(29)-en-28-oic acid methyl ester, 3α-acetoxy-27-hydroxylup-20(29)-en-28-oic acid methyl ester, and 3α-acetoxyolean-12-ene-27,28-dioic acid 28-methyl ester along with four known lupene-type triterpenoids from the roots of *Peganum nigellastrum*. They elucidated their structures by means of NMR techniques and only 3α, 27-dihydroxylup-20(29)-en-28-oic acid methyl ester (30) is a DNA topoisomerase II inhibitor that plays a crucial role in DNA metabolism [32].



(30)

Wada et al. screened naturally occurring lupane- and oleanane-type triterpenoids for human DNA topoisomerases I and II inhibitory activities and it was found that Olean-12-en-3β,15α-diol (31), olean-12-en-3β,15α,24-triol (32), lupeol (33), and betulin (34) showed significant activity to DNA topoisomerases II [33].



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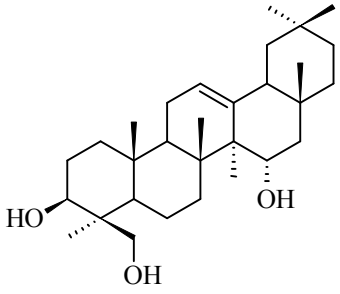

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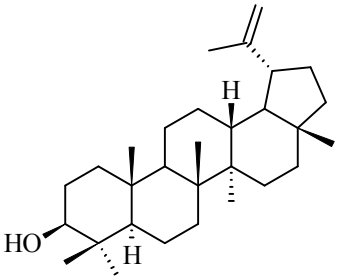

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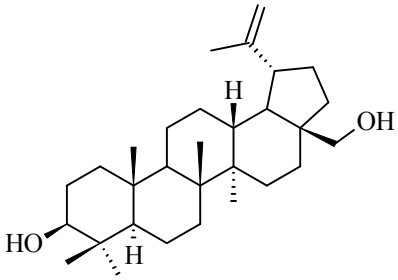
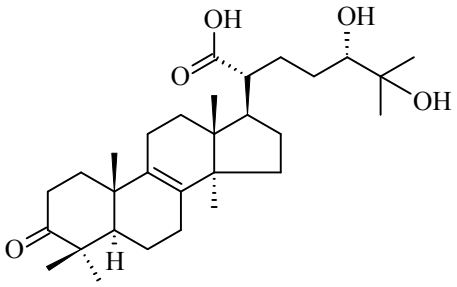


(34)

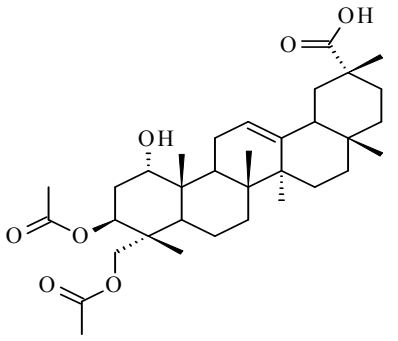
Yoshikawa et al. isolated two new lanostane triterpenoids and ten new lanostane triterpene glycosides from the fruit bodies of *Fomitopsis pinicola*. Their biological activity was investigated against COX-1 and COX-2 and compound (35) showed significant activities corresponding to indomethacin against COX-2 [34].



(35)

Oh et al. extracted two new ursane-type triterpenoids, 3α,19α-dihydroxyurs-12,20(30)-dien-24,28-dioic acid and 3α,19α-dihydroxyurs-12-en-24,28-dioic acid, together with 12 known ursane- and oleanane-type triterpenoids from the leaves of persimmon (*Diospyros kaki*). Triterpenoids with a 3α-hydroxy moiety were not active but with a 3β-hydroxy group were found to inhibit protein tyrosine phosphatase 1B (PTP1B) [35].

Litaudon et al. isolated 15 pentacyclic triterpenoids possessing olean-12-en-28-oic acid and olean-12-en-29-oic acid aglycons from the ethyl acetate extracts of the leaves and flowers of *Combretum sundaicum* and the leaves of *Lantana camara*. Only compounds (36-40) have binding affinity of the antiapoptotic protein Bcl-xL, capable of disrupting the Bcl-xL/Bak association [36].



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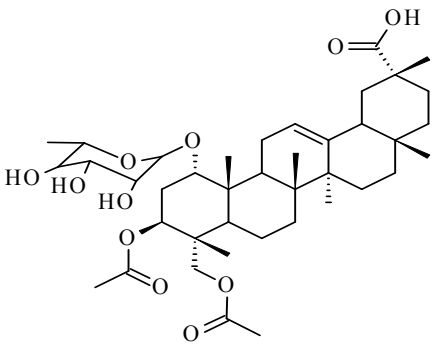

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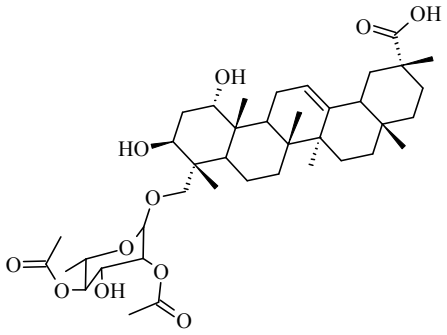

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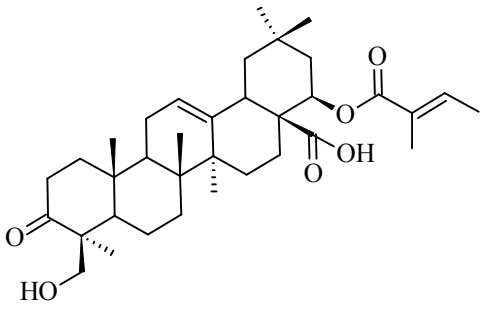

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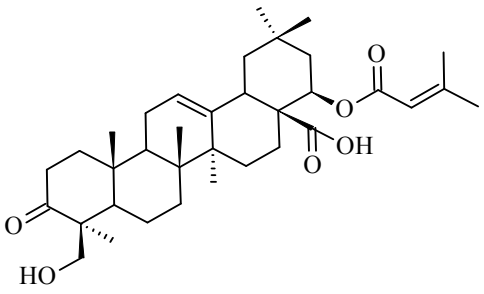
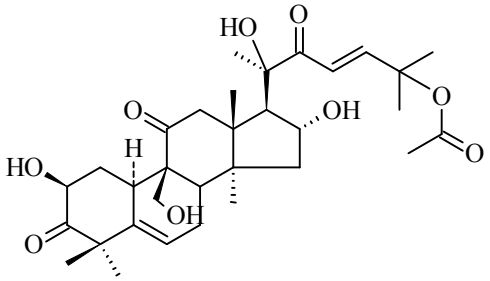


(40)

Zhao et al. isolated 21 cucurbitane-type triterpenoids from the stems of *Cucumis melo*. Their structures were elucidated on the basis of spectroscopic studies, chemical methods, and comparison with spectroscopic data in the literature. Two compounds, cucurbitacin A (41) and

cucurbitacin B (42), exhibited significant cytotoxic activity against the proliferation of A549/ATCC and BEL7402 cells in vitro [37].



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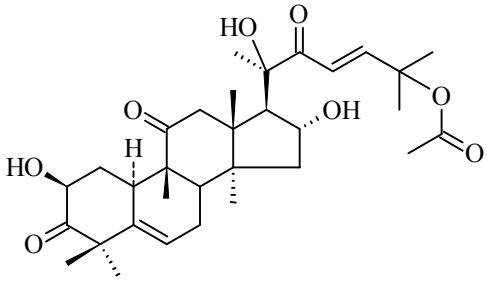
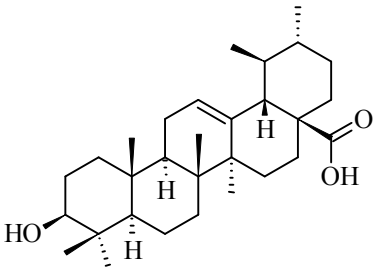


(42)

Li et al. investigated cytotoxicity and inhibition on human DNA topoisomerase I and II of 74 plant-originated triterpenoids and triterpenoid glycosides [38]. Soto et al. investigated the oral antidiabetic activity of four structurally-related triterpenic acids: ursolic (43), oleanolic (44), moronic (45) and morolic (46) acids and all compounds showed significant antidiabetic activity [39].



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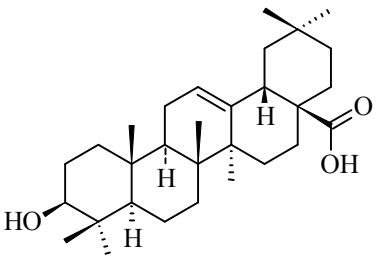

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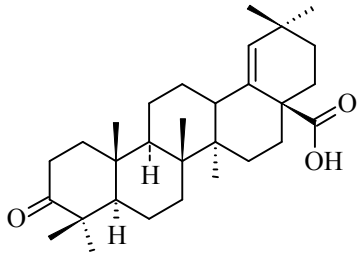

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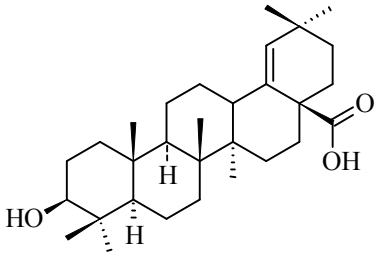
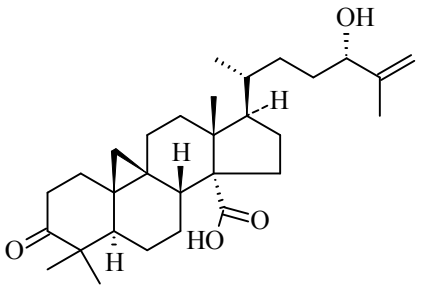
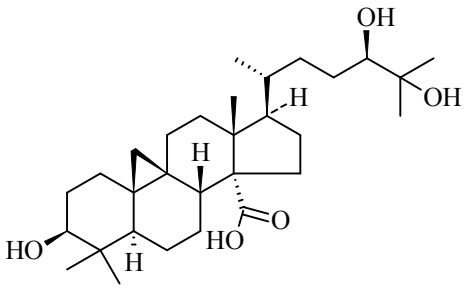


(46)

Hao et al. isolated five new triterpenoids, caloncobic acids A and B, caloncobalactones A and B, and glaucalactone, along with the known compounds 3β,21β-dihydroxy-30-nor-(D:A)-friedo-olean-20(29)-en-27-oic acid and acetyltrichadenic acid B from the leaves of *Caloncoba glauca*. Caloncobic acids A and B (47 and 48) exhibited strong inhibitory activities against mouse and human 11β-hydroxysteroid dehydrogenase type 1 which can influence factors affecting metabolic syndrome such as insulin resistance and dyslipidemia [40].



(47)

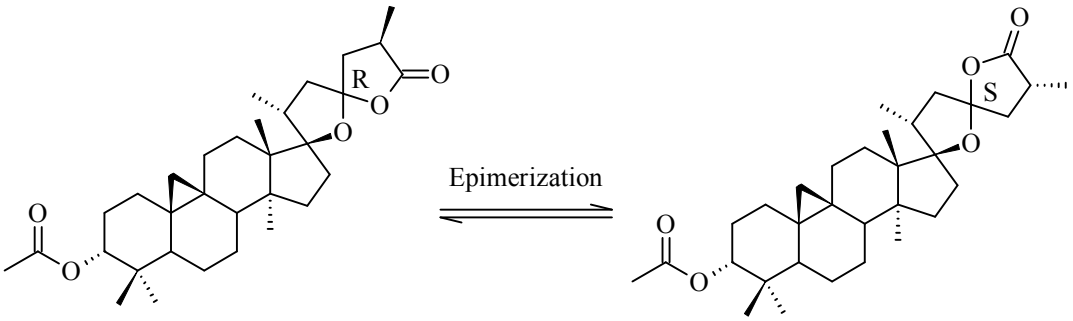


(48)

Shi et al. isolated five triterpenoids with a new 25-norfern carbon skeleton , a lupane triterpenoid, and four 20-hydroxyprogesterone acyl esters, together with 23 known compounds from the stem (with skin removed) of *Sinocalamus affinis*. These five triterpenoids with a new 25-norfern carbon skeleton exhibited inhibitory activity against protein tyrosine phosphatase 1B [41].

Yu et al. have reported that some of isolated novel iridal-type triterpenoids from the ethanol extract of the rhizomes of *Iris tectorum* exhibited neuroprotective activities against serum-deprivation-induced PC12 cell damage [42].

Eight pairs of epimeric triterpenoids were isolated from *Abies faxoniana* as inseparable mixtures of C-23 epimers in a specific proportion. It was stated that Compound 49 showed cytotoxicity against three hepatoma cell lines, namely, HepG2, Huh7, and SMMC7721 but exerted low cytotoxicity on normal QSG7701 hepatic cells, indicating its selective cytotoxicity for hepatoma cells [43].



49a 49b

2.2. Quantitative structure-activity relationships of bioactive terpenoids

The structure and reactivity relationship on a quantitative basis was introduced by Hammett (1935, 1937) where substituent effects on reaction mechanisms are explained by using two parameters namely substituent constant and reaction constant [44, 45]. In the 1950s, Taft proposed a way for separating polar, steric, and resonance effects of substituent in aliphatic compounds and introduced the first steric parameter, E_S [46]. The contributions from Hammett and Taft set forth the mechanistic basis for the development of the QSAR paradigm by Hansch and Fujita. (1964). Fujita and Hansch then constructed a linear equation (called Hansch linear

equation) by combining hydrophobic constants with Hammett's electronic constants [47, 48]. The failure of linear equations led to the development of the parabolic Hansch equation in cases with extended hydrophobicity ranges [49]. At the same time, Free and Wilson formulated an additive model of substituent contributions to biological activities, giving a push to the QSAR development [50].The quantitative structure-activity relationships have been further developed by Kier and Hall on their studies of connectivity indices based on hydrogen suppressed molecular structures [51-53]. Other popular QSAR approaches are HQSAR, Inverse QSAR, and Binary QSAR [54-57]. In 1988, Cramer et al. proposed 3D-QSAR methodology, Comparative Molecular Field Analysis (CoMFA) [58]. Other 3D-QSAR approaches have been developed, such as Comparative Molecular Similarity Indices Analysis (CoMSIA) [59, 60] or Self Organizing Molecular Field Analysis (SomFA) [61].

Jiang et al. used ether and ester analogs of artemisinin for comparative molecular field analysis (CoMFA) to correlate between the physicochemical properties and the in vitro activities. Four alignment models were used in this study and correlation study suggested that all to have good predictive values [62].

A three-dimensional quantitative structure-activity relationship paradigm was used by Chen et al. to correlate between the physicochemical properties and the in vitro bioactivities of ginkgolide analogues. They designed compounds on the basis of CoMFA analysis and it was found that three of these new designed compounds are more potent than that of ginkgolides [63].

Woolfrey et al. compared two 3D-QSAR methods, comparative molecular field analysis (CoMFA) and hypothetical active site lattice (HASL), with respect to the analysis of a training set of 154 artemisinin analogues. Five models including a complete HASL and two trimmed

versions, as well as two CoMFA models were created. Although the differences between CoMFA contour maps and the HASL output, each of the four predictive models exhibited a similar ability to predict the activity of a test set of 23 artemisinin analogues [64].

Heravi et al. carried out a quantitative structure-property relationship study based on multiple linear regressions (MLR) and artificial neural network (ANN) techniques to investigate the retention behavior of some terpenes on the polar stationary phase. A collection of 53 noncyclic and monocyclic terpenes were divided into two groups, a training set of 41 molecules and a test set of 12 molecules. A total of six descriptors containing one electronic, two geometric, two topological and one physicochemical descriptors were appeared in the MLR model and it has been found that electronic, topological and physicochemical descriptors have a pronounced effect on the retention behavior of the terpenes [65].

Grodnitzky et al. developed quantitative structure-activity relationships (QSARs) to predict insect toxicity of monoterpenoids and its derivatives. They found a linear relationship between house fly toxicity and Mulliken populations in aromatic monoterpenoids. Multiple linear regression study of an E-State descriptor and a GETAWAY (GEometry, Topology and Atomic Weights AssemblY) descriptor established a relationship with house fly toxicity for a number of monoterpenoids [66].

Artemisinin is an effective drug against chloroquine-resistant *Plasmodium falciparum* strains and cerebral malaria. Cheng et al. carried out molecular docking simulations to probe the interactions of artemisinin and its analogues with hemin and then performed 3D-QSAR study employing comparative molecular force fields analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA). Docking simulations provided probable bioactive conformations of

artemisinin analogues. The partial least squares (PLS) analysis suggests that the calculate binding energies correlate well with the activity values. The results of molecular docking and 3D-QSAR help to explain the binding model and activity of new synthesized artemisinin derivatives [67].

Kuriyama et al. performed comparative molecular field analysis (CoMFA) with thirteen seco-prezizaane terpenoids isolated from star anise species (*Illcium floridanum, Illcium parviflorum, and Illcium verum*) for their ability to inhibit the specific binding of [^{3}H]4'-ethynyl-4-n-propylbicycloorthobenzoate (EBOB), a non-competitive antagonist of gamma-aminobutyric acid (GABA) receptors, to housefly-head and rat-brain membranes. This 3D-QSAR study demonstrated that seco-prezizaane terpenoids can bind to the same site as do picrotoxane terpenoids such as picrotoxinin and picrodendrins. The CoMFA maps identified the parts of the molecules essential to high activity in housefly GABA receptors [68].

For the development of non toxic analogues of artemisinin, Avery et al. utilized comparative molecular field analysis (CoMFA) and hologram QSAR (HQSAR) with a series of 211 artemisinin analogues with known in vitro antimalarial activity. The bioactive conformation of artemisinin and its analogues were found by two ways: (i) X-ray structure of artemisinin and (ii) the hemin-docked conformation. The generated CoMFA and HQSAR models have excellent statistically properties and possessed good predictive ability for test set compounds [69].

Ghafourian et al. investigated the structural requirements of penetration enhancers using the Quantitative Structure-Activity Relationship (QSAR) technique. The possible mechanism of skin penetration of 5-fluorouracil, diclofenac sodium (DFS), hydrocortisone (HC), estradiol and

benazepril by naturally occurring terpenes, pyrrolidinone and N-acetylprolinate derivatives have been discussed [70].

Guha et al. developed QSAR models to predict the biological activity of 179 artemisinin analogues. They generated topological, geometric, and electronic descriptors for linear (multiple linear regression) and nonlinear (computational neural network) models to link the structures and biological activity. The best nonlinear model is superior to the best linear model in terms of pure predictive ability [71].

Schmidt et al. conducted a QSAR study of the seco-prezizaane-type sesquiterpenes pseudoanisatin and parviflorolide from *Illicium*. The compounds are noncompetitive antagonists at housefly (*Musca domestica*) γ-aminobutyric acid (GABA) receptors and show selectivity toward the insect receptor. This QSAR study provided insight into the structural basis of selectivity of seco-prezizaane-type sesquiterpenes and properties of the binding sites at GABA receptor-coupled chloride channels of insects and mammals [72].

Cortes-Selva carried out comparative molecular similarity indices analysis (CoMSIA), a three-dimensional quantitative structure-activity relationships with a number of dihydro-beta-agarofuran sesquiterpenes as modulators at the P-glycoprotein-like transporter. This 3D-QSAR study was employed to characterize the steric (contribution of 5.4%), electrostatic (58.9%), lipophilic (10.0%), and hydrogen-bond-donor (13.3%) and acceptor (7.5%) requirements of these sesquiterpenes with the receptor [73].

Siedle et al. investigated a set of 103 different sesquiterpene lactones for their NF-kappaB inhibiting properties and their activity values were submitted to a QSAR study [74].

Macias et al. carried out a quantitative structure-activity study with 34 guaianolides having different numbers of hydroxyl groups and ester side chains of variable length and structure to evaluate the effect of lipophilia/aqueous solubility on etiolated wheat coleoptiles elongation. Data show a strong influence of logP values [75].

Zhu et al. performed three dimensional quantitative structure-activity relationship studies employing comparative molecular fields analysis (CoMFA), comparative molecular similarity indices analysis (CoMSIA) and hologram QSAR (HQSAR) with a number of Ginkgolide analogues and their bioactivities against PAF receptor. Three rational and predictive QSAR models were constructed with high q^2 released ranging from 0.583 to 0.684. This study helps to understand the possible binding mechanism between ginkgolides and human PAF receptor and should be very useful in discovering new drugs as PAF antagonists [76].

Ishihara et al. observed that the cytotoxicity of betulinic acid derivatives can be predicted by heat of formation, hydrophobicity (log P), water solubility, ionization potential, electron affinity and dipole moment but not by molecular size. These parameters were determined by semi-empirical molecular-orbital method [77].

Two and three dimensional quantitative structure activity relationship models were constructed for a series of 20 butitaxel analogues (paclitaxel and docetaxel) to investigate the properties associated with microtubule assembly and stabilization. A CoMFA model was built using steric and electrostatic fields with $r^2 = 0.943$ and a cross-validated r^2 (i.e. q^2) = 0.376. Using the same data, HQSAR generated an $r^2 = 0.919$ and a $q^2 = 0.471$. All the analogues were docked into beta-tubulin model and their docking pose were nearly identical with paclitaxel bound to the protein.

A modest correlation (r^2 = 0.53) was found between activity and docking energy of all the butitaxel analogues in the dataset [78].

Comparative molecular field analysis (CoMFA), a three-dimensional quantitative structure-activity relationship (3D-QSAR) paradigm was used to observe effect of argentatin B derivatives on the growth of K562 cancer cell lines. This study indicated that the activity depends on bulky group at C-2, a C1-C2 double bond, and low electronic density at C-25 [79].

Sung et al. constructed QSAR models between oleanolic acid analogues and the inhibition activities of protein tyrosine phosphatase-1B (PTP1B) using 2D-QSAR and HQSAR methodologies. From the analysis results of these two models, the HQSAR was statistically better than 2D-QSAR [80].

Rasulev et al. studied quantitative structure-estrogenic activity relationship in a series of terpenoid esters with aromatic and aliphatic acid substituent isolated from Ferula plants. In this QSAR approach the data generated from three-dimensional structures of terpenoids and from quantum-chemical calculations at the B3LYP/6-31G(d, p) level of theory. A significant QSAR model with r^2=0.892 showed that the estrogenic activity depends on the parameters such as molecular shape, number of phenolic groups, surface polarity and the energy of the highest occupied molecular orbital [81].

Hemmateenejad et al. developed a quantitative structure property relationship (QSPR) for the Kovats retention indices of a large number of terpenoids [82].

Scotti et al. investigated a QSAR study of 37 different sesquiterpene lactones from the Asteraceae family with their cytotoxic activities. A single model was constructed using 3D

molecular descriptors and genetic algorithms which explained the important properties for the inhibition potency [83].

Chang et al. developed a quantitative structure-activity relationship model of eleven terpenoids with significant neuroprotective activity. This study indicated that the activity was mainly governed by lipophilicity, shape index, and electrostatic property [84].

Multidrug resistance is one of the major challenges in many diseases. Reyes et al. reported the inhibitory activity of a number of 76 dihydro-beta-agarofuran sesquiterpenes, tested on NIH-3T3 cells expressing the human P-glycoprotein (Pgp) multidrug transporter. A three-dimensional quantitative structure-activity relationship model using the comparative molecular similarity indices analysis (CoMSIA) was used to understand the structural basis for inhibitory activity and guide the design of more potent Pgp inhibitors [85].

The structural requirements of terpenes and terpenoids as penetration enhancers have been investigated by Kang et al. using the Quantitative Structure-Activity Relationship (QSAR) technique. In this work, the human skin penetration effect of 49 terpenes and terpenoids were compared by the in vitro permeability coefficients of haloperidol through excised human skin. They suggested that an ideal terpene enhancer must have at least one or combinations of the following properties: hydrophobic, in liquid form at room temperature, with an aldehyde or ester functional group but not acid group, and is neither a triterpene nor tetraterpene [86].

Setzer has been used molecular docking techniques to examine the potential binding sites of a number of triterpenoids inhibitors of topoisomerase II. The molecular docking results reveal that most of the triterpenoid ligands preferentially bind to the DNA binding site of topoisomerase II,

while a few also bind to the ATP binding site. This study gives some idea about the cytotoxicity of these natural products [87].

Breast cancer is one of the leading causes of death among women. Verma et al. used four series of taxane derivatives to correlate their inhibitory activities against breast cancer cells with their hydrophobic and steric properties to understand their chemical-biological interactions. This study suggested that the inhibitory activities of these compounds against breast cancers are mainly dependent either on their hydrophobicity or the hydrophobic/molar refractivity descriptor of their substituents [88].

Hansch et al. discussed the interaction of taxanes with the tubulin/microtubule system by the formulation of six QSARs. They suggested that hydrophobicity of the substituents and steric parameters are the important determinants of the activity. They believed that two QSARs models can help to provide guidance in design compounds that may have high biological activities [89].

Cardoso et al. studied the activity of artemisinin and some derivatives against D-6 strains of *Plasmodium falciparum*. They used molecular electrostatic potential maps to identify important features of the compounds and then use those to propose new artemisinin derivatives. The partial least squares (PLS) method was then utilized to produce a predictive model. They found that the important descriptors for construction of the model were the highest occupied molecular orbital energy, atomic charges on the atoms O1 and C3, molecular volume, and hydrophilic index [90].

Wang et al. synthesized a series of terpenoid compounds from alpha- and beta-pinenes. The antifeedant activities of these compounds were tested on the aphid, *Lipaphis erysimi* (Kalt.). The statistically best QSAR model suggested that the relative number of O atoms, HOMO-LUMO

energy gap, molecular volume, and total charge on the positively charged fragments were the important indices to predict the antifeedant activity [91].

Setzer was carried out quantum chemical calculations at the B3LYP/6-31G* level of theory on 20 celastroid triterpenoids to get a set of molecular electronic properties and to correlate these with cytotoxic activities. The cytotoxic activities of these triterpenoids may be roughly correlated with the energies of the frontier molecular orbitals (E_{HOMO} and E_{LUMO}), the HOMO-LUMO energy gap, the dipole moment, the charge on C(6), and the electrophilicity on C(6) [92].

In order to find out new taxane derivatives with fewer side-effects and improved anticancer activity, Verma et al. correlated their inhibitory activities against lung cancer cells with hydrophobic and steric descriptors for understanding their chemical-biological interactions. On the basis of this QSAR study, six compounds were suggested as potential synthetic targets [93].

Steinmetz et al. conducted 3D-QSAR studies of trichothecene mycotoxins, toxic natural products of fungi from the family *Hypocreaceae*, are potent inhibitors of protein synthesis. They explained the role of electrostatics and steric factors in the activity of the toxins and show that the conformation of the macrolide ring influences the toxicity of the macrolide toxins [94].

Schmidt et al. conducted a QSAR study on a set of 40 sesquiterpene lactones against *T. brucei rhodesiense* (which causes East African sleeping sickness), *T. cruzi*, *Leishmania donovani* and *Plasmodium falciparum* [95].

Hansch et al. conducted QSAR studies on a series of C2-modified 10-deacetyl-7-propionyl cephalomannines with respect to their binding affinities toward beta-tubulin and cytotoxic activities against both drug-sensitive and drug-resistant tumor cells. The drug resistance is mediated through either P-glycoprotein overexpression or beta-tubulin mutation mechanisms.

This study suggested that hydrophobicity and molar refractivity are the important parameters for the activity. They believed that two QSAR models may provide guidance in design and synthesis of cephalomannine derivatives that may have high biological activities [96].

Saiz-Urra et al. performed quantitative structure-activity relationship (QSAR) studies using a topological sub-structural molecular design (TOPS-MODE) approach of twenty-three clovane derivatives with their in vitro antifungal activity against the phytopathogenic fungus *Botrytis cinerea*. The most important parameters were the spectral moments weighted by bond dipole moment, hydrophobicity, and the combined dipolarity/polarizability Abraham molecular descriptor [97].

Little et al. performed docking and QSAR study of a series of artemisinin derivatives. The Heme molecule receptors were primarily selected to represent the changing binding and oxidation states of the molecule and relate these results to the observed biological activity [98].

Xu et al. conducted 2D and 3D QSAR studies on andrographolide derivatives as α-glucosidase inhibitors. They used 25 andrographolide derivatives as a training set and recommended that the combination of 2D and 3D QSAR models might be useful in predicting the alpha-glucosidase inhibiting activity of andrographolide derivatives [99].

Badawy et al. conducted QSAR studies of monoterpenes against the two-spotted spider mite, *Tetranychus urticae*. The QSAR model showed brilliant agreement between the predicted and experimentally measured toxicity parameter for the tested monoterpenes [100].

For the development of taxane analogues with improved anticancer activity and fewer side effects, Verma et al. performed QSAR modeling of taxane derivatives against colon cancer. The results of the study suggested that the steric and hydrophobic parameters of the substituents are

the two most important determinants for the activities of taxane analogues against colon cancers [101].

McGovern et al. constructed two CoMFA models of Salvinorin A analogs substituted at the C-2 position at the kappa-opioid receptor. They employed three alignment methods: a receptor-docked alignment derived from GOLD algorithm, the ligand-based alignment from FlexS algorithm, and a rigid realignment of the poses from the receptor-docked alignment. The first algorithm i.e. receptor-docked alignment produced statistically better results compared to either the FlexS alignment or the realignment. From the CoMFA contour maps, the binding mode of amine-containing Salvinorin A analogs was proposed and suggested that the beta-epimers (R-configuration) of protonated amines at the C-2 position have a higher affinity than the corresponding alpha-epimers (S-configuration) [102].

Hassan et al. proposed 3D-QSAR studies of eunicellin-based diterpenoids which showed significant anti-migratory and anti-invasive activities against prostate cancer in wound-healing and Cultrex invasion models. They created a valid 3D-QSAR model for guiding the design of potent eunicellin diterpenes cancer migration inhibitors [103].

Bharate et al. carried out QSAR study for a series of phloroglucinol-terpene adducts exhibiting anti-leishmanial activity and suggested that the lipophilic character (CLogP), isoelectric point, Haray index and Platt index play important role in anti-leishmanial activity [104].

A number of betulinic acid and betulin derivatives with anti-HIV-1 activities were used to perform 3D-QSAR studies by using CoMFA and CoMSIA. The analysis A and analysis B of this study were related to two activity indexes EC_{50} and TI (therapeutic index) respectively. The analysis A which was resulted from 41 molecules produced r_{cv}^2 values of 0.664 and

0.718, r^2 values of 0.979 and 0.955, respectively. The analysis B resulted from 41 molecules provided r_{cv}^2 values of 0.570 and 0.559, r^2 values of 0.938 and 0.933, respectively. The contour maps illustrated the regions in space where interactive fields may influence the activity. The results may be used for the design of potential betulinic acid and betulin derivatives with better anti-HIV-1 activity [105].

In order to predict the structural features responsible for α-glucosidase inhibitory activity, Moorthy et al. performed a QSAR analysis on a series of andrographolide derivatives. They used subdivided surface area, adjacency, surface volume and shape, partial charge descriptors and found a high correlation with the inhibitory activity [106].

Lan et al performed 3D-QSAR and molecular docking studies of betulinic acid derivatives that are responsible for the anti-HIV activity [107].

Wei et al. performed 3D-QSAR studies of a set of 43 natural sesquiterpene polyol esters with optimal narcotic or insecticidal activities. The 3D-QSARmodels suggested that the electronic effect governs the narcotic activities where as the combination of electrostatic and hydrophobic interactions are more influential in the insecticidal activities of the molecules [108].

Zhao et al. studied a QSAR study of a series of tanshinone compounds with cytotoxicity against murine leukemia cell lines P-388 using density functional theory. They used four indices: the maximum molecular electrostatic potential at the SAS surface, the average nucleophilic superdelocalizability, the dihedral between ring A and B and the net atomic charge of C (12). They constructed QSAR equation via multiple linear regression analysis and based on this model they designed compounds theoretically [109].

Bartalis et al. conducted QSAR studies to evaluate cucurbitacins (Cucs) liver protective activity in vitro against lipophilicity and ab initio descriptors [110].

Liang et al. performed receptor-based 3D-QSAR studies of 106 naturally occurring pentacyclic triterpenes as glycogen phosphorylase inhibitors. This study suggested that the elongated or bulky substitutions in C17 position and/or C2, C3 positions of pentacyclic triterpenes are favorable. They synthesized 56 compounds and evaluate their activity [111].

Maurya et al. performed QSAR modeling and docking studies of two triterpenoids ursolic acid and lupeol isolated from *Eucalyptus tereticornis* and *Gentiana kurroo*. This study suggested that both the triterpenoids show anti-inflammatory activity due to high binding affinity to human receptors viz., NF-kappaB p52 and may be considered as potential immunomodulatory drug-like molecules [112].

Tong et al. determined two QSAR models of monoterpenoids which have insecticidal potency on pest insects. This study suggested that the hydrophobicity and stability of monoterpenoid molecules were strongly involved in binding activities to the housefly GABA receptor [113].

Kalani et al. developed QSAR models for predicting the activities of ursolic acid analogs against human lung (A-549) and CNS (SF-295) cancer cell lines by a forward stepwise multiple linear regression method using a leave-one-out approach. This study indicated that the LUMO energy, ring count, and solvent-accessible surface area were strongly correlated with anticancer activity. Some ursolic acid analogs were semisynthesized based on QSAR results and tested in vitro against the human lung (A-549) and CNS (SF-295) cancer cell lines [114].

Abbasitabar et al. derived QSAR models for 179 analogues of artemisinin, a potent antimalarial agent. The reactive and partial equalization of orbital electronegativity descriptors represented the highest impact on the antimalarial activity [115].

Wang et al. performed CoMFA studies on 37 betulinic acid and betulin derivatives and their in vitro anti-cancer activity results against HT29 human colon cancer cells. The study provided a leave-one-out cross-validation q2 value of 0.722 and a non-cross-validation r^2 value of 0.974, which suggested that the model has good predictive ability (q2 > 0.2). The contour maps suggested that bulky and electron-donating groups at the C-28 site and a moderately bulky and electron withdrawing group near the C-3 site would improve the activity. Three betulin derivatives were designed and synthesized and their in vitro cytotoxicity was consistent with the predicted values. Thus the present topomer CoMFA model could guide the synthesis of new betulin derivatives with high anti-cancer activity [116].

Song et al. studied the interactions between low-toxicity terpenoid mosquito repellents and lactic acid at the HF and B3LYP level. This study suggests that the repellent-lactic acid complexes may play an important role [117].

Sousa et al. applied QSAR methodology to identify the most relevant molecular features of macrocyclic diterpenes with P-glycoprotein inhibitory activity. They developed a QSAR model for a set of 51 bioactive diterpenic compounds which includes lathyrane and jatrophane-type diterpenes and another model just for jatrophanes [118].

A QSAR study was performed of the antimalarial agent artemisinin and some of its derivatives using DFT based descriptors such as hardness, chemical potential, electrophilicity index, Fukui function, and local philicity. Multiple regression analysis was performed to construct QSAR

model using these descriptors against the chloroquine-resistant, mefloquine-sensitive Plasmodium falciparum W-2 clone [119].

Schomburg et al. investigated a QSAR model of natural sesquiterpene lactones as inhibitors of Myb-dependent gene expression. This QSAR approach was based on flexible alignment method [120].

Liao et al. in 2014 studied molecular interactions between terpenoid mosquito repellents and three typical human-secreted attractants, ammonia, 1-octen-3-ol, and formic acid. Relative energies, bond distances, and bond angles of the molecular interactions at HF level were used in the study in order to understand the relationship among mosquito repellents and attractants secreted by human hosts [121].

Foudah et al. conducted pharmacophore modeling and 3D-QSAR studies of sipholane triterpenoids as breast cancer migration and proliferation inhibitors [122].

Rudnitskaya et al. developed 3D-QSAR models of fifteen sesquiterpenoids, relating the hepatoprotection activity with molecular properties. Different chemical features such as shape, branching, symmetry, and presence of electronegative fragments can regulate the hepatoprotective activity of these sesquiterpenoids [123].

Trossini et al. constructed HQSAR models of 40 sesquiterpene lactones with activity against *T. brucei, T. cruzi, L. donovani and P. falciparum* (antiprotozoal activities) and also with their cytotoxicity. The differences between the most and least potent compounds were found from HQSAR contribution maps. This study also suggested as previous QSAR study that the presence of the α,β-unsatured carbonyl groups is fundamental to biological activity of sesquiterpene lactones [124].

Cheng et al. synthesized 21 novel sesquiterpenoids, trichodermin derivatives containing conjugated oxime ester and screened for in vitro antifungal activity. They performed QSAR analysis with these compounds and found that log P and hardness were two critical parameters for the biological activities [125].

Thanashankar et al. have performed the pharmacophore modeling and 3D-QSAR studies of a series of amino alkyl rupestonates (Rupestonic Acid) derivatives which inhibit H1N1, H3N2 and influenza B virus. In order to improve the biological activity of these compounds, a four point pharmacophore model with one acceptor and three hydrophobic regions was developed. On the basis of pharmacophore hypothesis, the 3D-QSAR model was constructed which provided an invaluable insight into structure activity correlation [126].

Appell et al. evaluated 35 trichothecenes using density functional theory at the 6-311+ G (d,P) level of theory. Type A and type B trichothecenes have distinct quantum-based differences including their frontier molecular orbital and natural bond orbital properties. QSAR models were constructed using one and two dimensional descriptors to describe cytotoxicity, phytotoxicity, and detection cross-reactivity. The important components of the models were topological indices and electronegativity [127].

Andrographolide, the labdane diterpene, isolated from *Andrographis paniculata*, has several pharmacological activities including immuno-stimulatory, cytotoxic, anti-inflammatory, anticancer, hypotensive, cardio-protective and anti-HIV. Mondal et al. synthesized a number of andrographolide derivatives and performed 2D QSAR study which indicates that steric effects and van der Waals interactions play major roles in the determination of antiproliferative activity

of these compounds. 3D QSAR study revealed that the benzyl substitution at N20 position may be important for higher steric interaction [128].

Artemisinin possesses anticancer activity through anti-angiogenic effects. Efferth et al. performed molecular docking of 52 artemisinin derivatives to vascular endothelial growth factor receptors (VEGFR1 VEGFR2), and VEGFA using Autodock4. They also performed QSAR study with these compounds [129].

Tiwari et al. performed QSAR study with a number of gymnemic acid analogues against PPARγ, a promising drug target for diabetes. In this study they found that chemical descriptors viz., dipole moment, electron affinity, dielectric energy, secondary amine group count and LogP correlated well with the activity and provides an insight into the therapeutics for diabetes mellitus [130].

A series of 30 compounds which are structurally related to geranyl acetone, nerolidol, farnesal, farnesol and farnesyl acetate, are potentially useful in fragrance compositions as antimicrobial agents and showed better or comparable activity to parent terpenoids. The generated pharmacophore models, obtained by 3D QSAR modeling, indicate significant steric factors which determine the antimicrobial activity of the compounds [131].

Essential oils and their constituents are known for their wide variety of biological activities such as antibacterial, antifungal, antiparasitic and antimycobacterial properties. Rivera-Chavira et al. was evaluated the descriptor of the molecular properties and the structural characteristics responsible for antimycobacterial activity of the tested compounds and developed QSAR models. These descriptors provide insight into the mechanisms of action of the active molecules and help to synthesize active compounds [132].

2.3. References

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