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Review

Quantitative Structure-Activity Relationship of Alkaloids with Immunomodulatory Effects

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Abstract: Natural products are considered an essential source of chemical compounds with relevant biological activities. Important antibiotics, anti-virals, and anticancer agents within healthcare facilities have been isolated from them. In recent decades, the study of alkaloids and the modulation of the immune response has aroused interest. The survey of SAR alkaloids with immunomodulatory effects is of great importance since structural modifications impact the effectiveness of the immunomodulatory activity, thus promoting the rational design of more effective and specific drugs. This review exhibits the main alkaloids with an immunomodulatory effect and their relationship with SAR studies, particularly in activating leukocytes and secretion of molecules with critical inflammatory activities such as cytokines, chemokines, and nitric oxide. These studies optimize the properties of alkaloids and allow a deeper understanding of the mechanisms of action at a molecular level, which is fundamental for the innovation of immunological therapies.

Keywords: alkaloids; secondary metabolites; structure-activity relationship; immune system; immunomodulatory

1. Introduction

All living cells produce metabolites due to their biochemical process during metabolism; one of the most studied is phytochemicals, considered primary and secondary metabolites and exhibit a comprehensive chemical composition and structural features [1]. Regarding plant physiology, secondary metabolites are involved in several mechanisms such as defense, signaling, and regulation [2,3]. Additionally, they are related to enhancing diverse cellular pathways such as cell activation and proliferation [4,5]. Their constant existence in nature results in a highly attractive chemical compound as a source of new drugs [6].

Therefore, natural products, including plants, animals, and fungi, have been a source of natural treatment for diverse diseases. They represent an essential fraction of drugs used in health facilities. They are characterized by their enormous and complex structural and physicochemical diversity, including rigid or semi-rigid cyclic features, proton donors and acceptors, and chiral centers [6,7]. For this reason, natural products can be categorized into phenolic compounds, polyketides, terpenoids, and alkaloids [8,9].

About 40,000 alkaloids are known and present structural features involving heterocyclic rings and a nitrogen atom and they are currently of great pharmacological importance. Since a significant source of alkaloid skeleton is derived from amino acid metabolism, they could be classified according to their precursors based on the biological pathway used to build the molecule [10,11]. Therefore,

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could be categorized into three large groups: true alkaloids, protoalkaloids (both derived from amino acids) and pseudoalkaloids (not derived from amino acids) [12–15]. They present a broad spectrum of biological activities such as anti-microbial [16–18], anti-viral [18,19], anti-diabetic [20], anti-carcinogenic [8,9,18,21–23], antioxidant [24], anti-parasitic [25]. Additionally, they are widely related to improving diverse biochemical factors during nervous, cardiovascular, and chronic degenerative diseases, such as diabetes and high blood pressure [26–28]. Alkaloids from the indole family contain chemotherapeutic drugs, such as Vinblastine, that present structural features intervening with cellular mechanisms by inhibiting the formation of spindle fibers, responsible for chromosome alignment and separation in anaphase promoting a decrease of cancer cells during mitosis [26,29–32].

Cyclic structures, such as chalcone [33], isoflavone [34] coumarin [35], are present in several alkaloid groups with pharmacological properties (Figure 1). For example, the quinoline ring, isoquinoline [36], indole [37], and pyrrolidine [38], function as chemical skeletons that are used for the development of new drugs [20] (Figure 1). For this reason, the knowledge of the chemical structure of a natural product and its biological activities has gained importance regarding new drug design in the last decade [39].

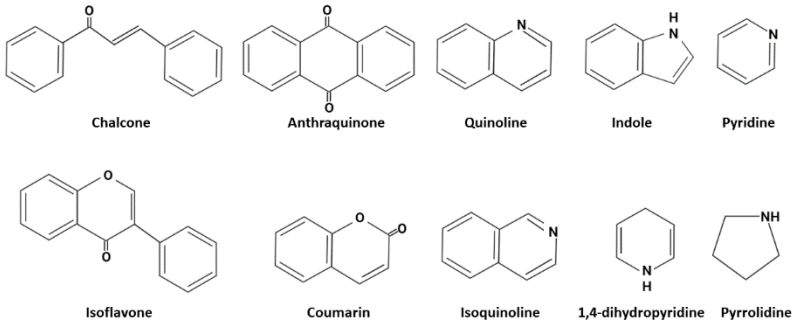

Figure 1. Heterocyclic structures are most used in new drug development. Cyclic structures, such as chalcone, isoflavone, and coumarin, are present in several alkaloid groups with pharmacological properties.

Although diverse alkaloids have shown biological activities, generating new chemical entities with less toxicity, side effects, and selective activity can develop by studying the structure-activity relationship (SAR) [4,40]. The intermolecular interactions between an alkaloid and a biologically important molecule, such as a hormone receptor, DNA, or ribosome, can be accomplished if the target structure is known, and computational chemistry and molecular modeling software packages can be useful in identifying binding site interactions [40].

SAR is often observed through computational chemistry and modeling software (if the chemical compound is known) and non-computational methods if the chemical compound is not known, such as synthesis of structure variants adding or removing functional groups. For in silico studies, parameters such as the number of rotary bonds, chiral centers, a fraction of Csp3 atoms, cyclic motifs, aromatic rings, nitrogen and oxygen atoms, number of hydrogen acceptors and donors, the number of acidic and basic atoms are considered [4,40]. Physicochemical properties are also included due to their essential role in the selective activity of natural compounds, such as solubility in organic or inorganic solvents. Interestingly, in an in vivo scenario, they may determine the absorption, distribution, and drug metabolism [22].

Currently, computer tools help predict and investigate the biological activities of compounds according to specific molecular characteristics. Using in silico analysis facilitates the modification of molecules or the design of new drugs, giving quantitative results for each molecule and particular activity according to descriptors based on geometric, topological, physical-chemical, and constitutional algorithms. As it is associated with subsequent in vitro studies, the efficacy of these new entities can be evaluated [41,42]. Diverse approaches in drug design have been used, such as structure-based, ligand-based drug design, and virtual detection. They are based on a target

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macromolecule or receptor that interacts with a drug, accelerating the entire process of discovery of chemical entities [43]. Structure-based drug design is performed with available structural models of the target molecule, which are obtained by X-ray diffraction [44], nuclear magnetic resonance (NMR) [45], or molecular simulation [46]. Once this information is obtained, the software analyzes the physicochemical properties of the receptor's drug-binding sites, followed by searching for existing molecules compatible with the receptor or the design of a new drug [43]. Ligand-based drug design is established by collecting known molecules that bind to the target macromolecule of interest [47], instead of structure-based drug design, which considers the receptor structure. The minimum necessary structural characteristics that a molecule must possess to bind to the target are defined using these known molecules. Likewise, this information can be used to build a model with Quantitative structure-activity relationship (QSAR) and predict the molecule's activity [43]. Virtual detection is essential for computer-aided drug design since identifying potential drugs is faster and cheaper than conducting trial-and-error experimental studies [48]. To date, there are many known alkaloids with immunomodulatory effects; however, more studies need to be conducted that include SAR analysis.

The modulation of the immune system by natural products, such as alkaloids or synthetic products, has gained importance in recent years due to its fundamental importance during new drug development [40–45]. Alkaloids are essential in immunomodulating intracellular signaling pathways involving inflammation responses by inducing inflammatory cytokines, cell proliferation, cell cycle arrest, T-cell activation, leukocyte recruitment, and adhesion molecule expression. These are through activating signaling pathways such as MAPK and JAK/STAT, which trigger inflammation transcription factors NFkB and AP-1 [6]. During an immune response, the role of these mediators impacts the recruitment of leukocytes, mainly neutrophil cells, in the infection site to eliminate foreign agents and then promote effector T or B cell homeostasis, leading to an inflammatory response regulation [7,49]. Thus, cancer-linked inflammation is essential in cancer development [6]. Chronic inflammation leads to loss of tissue structure and remodeling and oxidative stress by protein and DNA modification, increasing cancer risk development [50,51]. Additionally, during cancer development, inflammatory molecules such as reactive oxygen species, cytokines and chemokines, among others, may be derived from tumor-immune infiltrated cells. This review summarizes studies of QSAR of several alkaloids and their derivates regarding immunomodulatory activity, exposing the importance of developing more effective drugs with fewer side effects.

Chemical Modification

Synthetic and semi-synthetic compounds that explore biological activities in a dependent and rational manner are essential for drug discovery. To fully understand the immunological implication of alkaloids and their derivates on the host immune system, chemical modification has been made to study activity-structure relationships, aiming to improve the pharmacological properties based on activity-structure relationship analyses [31]. These modifications are established on drug modulation and structure-activity relationship analysis principles using different methods such as conventional reactions, combinatorial chemistry, and biotransformation [7].

The most frequent addition of functional groups that are found in drugs nowadays employed are hydrocarbon structures such as methoxy (OCH_3), ethoxy (OCH_2CH) isopropoxy [$OCH\ (CH_3)_2$], or methylenedioxy (OCH_2O) groups, as well as other functional groups such as esters (RCOOR'), amides (NH_2, NHR or NRR), sulfonates ($R\text{-}SO_3\text{-}$), aminomethyl (MeN), sulfonamides ($\text{-}SO_2N<$), hydroxyls (OH) or halogens (Br, Cl). Therefore, the structural modification of compounds, in many cases, potentiates their biological activities with capacities even superior to the native natural product from which they come naturally [7].

Alkaloids with immunomodulatory effects and QSAR evaluation

Since alkaloids are molecules of high pharmacological interest, they have been studied for their wide range of biological activities, as previously described. Therefore, the characterization of their chemical structures and their synthetic derivates is an attractive study subject for designing new immune response modulation drugs (Table 1).

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Table 1. Classification and Biological activities of Alkaloids with QSAR and Immunomodulatory effects.

Classification	Derivates	Compound	Activity	References
True alkaloids	Aspartate	Pyridine-linked hydroxylated Indanones	Anti-Inflammatory Bowel Disease	53
	Phenylalanine and Tyrosine	Berberine	Anti-proliferative, anti-bacterial	51, 58
Protoalkaloids	Tryptophan Indole	Phidianidines	Cytotoxic, Neuroprotective dopamine transporter inhibitory and protein tyrosine phosphatase-1B inhibitory	59
		Ellipticine β-carboline	Immunomodulation	60, 61 62
Pseudoalkaloids	Diterpenoid	songorine, delsolin, and fulzulin	NO Inhibition	63

True Alkaloids

True alkaloids are structurally complexes that derive from cyclic amino acids and are characterized by intracyclic nitrogen. They derived from amino acids such as L-ornithine, L-tyrosine, L-phenylalanine, L-lysine, L-histidine, L-tryptophan, L-arginine, and glycine/aspartic acid [11,13,14,52].

Aspartate-derived alkaloids are valuable compounds for pharmaceutical research and drug development due to their diverse biological activities (Table 1). A representative member of this family with QSAR and immunomodulatory effect is the indanone scaffold. This molecule is considered a privileged structure in medicinal chemistry. Indanone and its hydroxylated derivatives are well-documented for their diverse biological activities, such as anti-inflammatory and anti-cancer properties [53,54]. During inflammatory bowel disease (IBD) in vitro and in vivo [53], pyridine-linked indanone derivates were used to evaluate the inflammatory response by measuring cytokine tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine strongly related during IBD by enhancing inflammation through leukocyte recruitment to the infected site. Interestingly, pyridine-linked indanone derivates with methoxy, ethoxy, or isopropoxy groups induced a strong activity inhibiting TNF-α in monocyte adhesion by HT-29 colon epithelial cells. Additionally, in an induced rat colitis model, this derivates enriched colitis by altering the expression of inflammatory cytokines such as IL-1β, TNF-α, and the calcium-dependent cell-cell adhesion molecule, E-cadherin with pivotal roles in epithelial cell behavior, tissue formation, and suppression of cancer [53]. These results suggest that these compounds can reverse the damage and dysfunction caused by chronic inflammation, highlighting their therapeutic potential in clinical contexts. Suggesting that pyridine-linked indanone derivates can interfere with critical inflammatory pathways, making them promising candidates for new treatment development for IBD and other inflammatory diseases. Understanding how these compounds modulate the immune response at the molecular and cellular levels can provide valuable insights into specific mechanisms of action. This is crucial for optimizing drug design, improving efficacy, and minimizing side effects.

Several phenylalanine and tyrosine-derived alkaloids exhibited a broad significative pharmacological activity, such as the analgesics morphine and codeine, as the immunomodulatory Berberine, the latter being an essential representative family member of the Isoquinoline alkaloids.

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Berberine is one of the most studied alkaloids of this family for its anti-proliferative [51,55], antimicrobial [16,18], anti-diabetic [56] and anti-inflammatory properties [51,57], making it a molecule of great biological interest. Berberine derivatives with substituents with esterification (C3) and the addition of esters, amides, and sulfonates at position C9 down-regulated IFN-γ-induced promoter activity on the enzyme indoleamine 2,3-dioxygenase (IDO1) in A-549 human cancer cell line [58]. SAR studies indicated that large volume substituent at the 9-position is beneficial for enhancing the suppression of IFN-g-induced IDO1 promoter. INF-γ is a cytokine that is produced by activated T and NK cells and plays a crucial role in regulating various immune responses, as macrophage activation and enhancement of antigen presentation and therefore in the context of chronic inflammatory diseases, such as autoimmune, is often involved in the pathogenesis as tissue damage. Additionally, to elucidate the possible mechanism of action of the derivatives, their immunosuppressive effect was evaluated by acting on IDO1 by western blot. Several berberine derivates suppressed IFN-γ-induced IDO1 expression by activating AMPK by inhibiting STAT1 phosphorylation, demonstrating its relevance as a potential cancer immunotherapy drug [58].

Protoalkaloids

The principal structural feature of protoalkaloids is that they present a nitrogen atom but are not part of the heterocyclic ring and they may be derived from amino acids as L-tyrosine and L-tryptophan or amines [8,13,15,52]. Several indol alkaloids exhibited a broad biological activity, such as anti-microbial, antiproliferative, and anti-inflammatory, making this compound of interest in medicine and the pharmaceutical industry. One of the most studied regarding immunomodulation with SAR is phidianidines A and B. Isolated from marine sources presents diverse biological activities such as cytotoxic, neuroprotective, dopamine transporter inhibitory, and protein tyrosine phosphatase-1B inhibitory activities. Thirty-two phidianidines derivates were synthesized and the immunosuppressive activity of murine splenocytes was analyzed by measuring murine T and B-cell proliferation and analyzed by SAR [59]. Two derivates exhibited that the 1,2,4-oxadiazole ring and the 3,4,5 trimethoxyphenyl ring substitution played an essential role in the activity since they showed a highly inhibitory activity on T and B cell proliferation. In other studies, stimulated anti-CD3/CD28 antibody T-cells mimic the physiologic cross-linking of TCR. The results show that both derivatives suppress the proliferation of $CD4^+$ T-cells, the secretion of IL-2 and IFN-γ, and the presence of CD25. For B-cell function, the derivates strikingly inhibited $CD19^+$ B lymphocytes and showed regulatory effects on cytokine production, decreasing IL-6 and increasing IL-10 secretion. Phidianidine derivatives exhibited a potent immunosuppressive effect in vitro, including T and B-cell proliferation, activation and cytokine production. These chemical additions are essential for the immunomodulatory effect of these alkaloids, and due to their immunosuppressive effects and low toxicity, they are candidates for future in vivo research in immunological diseases [59].

Another important tryptophan-derived alkaloid is heterotetracyclic ellipticine, which presents diverse biological activities and immunomodulatory effects. Ellipticine derivates were synthesized [sodium bromo-5,11-dimethyl-6H-pyrido[4,3-b] carbazole-7-sulfonate (Br-Ell-SO3Na)] and studied SAR regarding immunomodulation [60]. The cytotoxicity of Br-Ell-SO3Na was tested in K562, Vero cell line and PBMC, the immunomodulatory activity was analyzed by measuring diverse interleukins. Ellipticine derivate Br-Ell-SO3Na showed the up-regulation of IL-6. This cytokine is related to various inflammatory and autoimmune diseases and, during acute inflammation, induces leukocyte recruitment, mainly neutrophils, to the infection site by regulating adhesion molecules and chemotaxis and stimulating the differentiation of T and B-cells, among others. Additionally, Br-Ell-SO3Na inhibited the expression of IL-8, a chemokine that, during cancer development, is associated with metastasis, angiogenic response, proliferation, survival, and migration of vascular endothelial cells. Both are pro-inflammatory biomarkers and are usually stimulated together during disease [60].

By QSAR and Docking, ellipticine derivates have been analyzed on three different proteins with high significance during leukemia as SYK (spleen tyrosine kinase), PI3K (phosphoinositide 3-kinase), and BTK (Bruton's tyrosine kinase), selected by their relevance during preclinical models. Derivates showed a high activity binding regarding their molecular structure, and several modifications were made to enhance their biological activity. Mainly, ellipticine derivatives with a hydrophobic

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substituent like a benzene ring increased the antileukemia activity (compound 9), and an aromatic ring bound to the ester moiety enhanced the biological activity (compound 22) [61].

Another member of the Indole alkaloids is β-carboline. By 3D-QSAR, several derivates were designed [62] and evaluated regarding the immunomodulatory effect in macrophages RAW 264.7, and the relationship between the chemical structure and anti-inflammatory impact was shown in several derivates by inhibiting nitric oxide (NO) production. NO is crucial for the proper functioning of macrophages. It enhances their ability to combat pathogens, regulates inflammation, influences macrophage activation and migration, promotes tissue repair, and plays a role in apoptosis and cytotoxicity. The balanced production and regulation of NO are essential for effective immune responses and maintaining tissue homeostasis. Thus, β-carboline alkaloid derivates present an attractive potential pharmacological agent with immunosuppressive potential [62].

Pseudoalkaloids

This group of alkaloids is not necessarily derived from amino acids; several pseudoalkaloids have nonamino acid precursors, and others are derived from transamination or amination reactions [15,52]. Diterpenoid alkaloids have been studied regarding their anti-inflammatory activity using QSAR to obtain molecular structure parameters and establish a predictive model for measuring the maximum mean effective concentration (EC50) [63]. With QSAR analysis, three diterpenoids songorine, delsolin, and fulzulin were studied, with EC50 of 0.301, 4.0517, and 3.8805 respectively, a lower value of EC50 indicating a more significant activity of the compound. Microglial cells (N9) were stimulated with LPS to analyze the anti-inflammatory effect and evaluate the NO release. Songorin inhibited NO production in LPS-activated N9 cells, dose-dependent, without apparent cytotoxicity, suggesting that it could be a potential inflammatory inhibitor, according to the model prediction (Log (EC50) = 0.301). However, fuzilin and delsolin did not exhibit inhibitory effects at the concentrations tested, according to the predicted value of the model [63]. QSAR is one of the models to help predict biological activities for new drug candidates.

Several natural products, semi-synthetic or synthetic entities exhibited a broad spectrum of biological activities. These are attributed to the chemical structure, presenting relevance during new drug design with less toxicity, side effects, and selective activity. In this review, we concentrated on studies that evaluated alkaloids with immunomodulatory effects and made a SAR analysis. The SAR analysis is of great interest; developing new molecular molecules to synthesize drugs with greater selectivity and less toxicity is necessary.

2. Conclusion

The study of the SAR of alkaloids and their derivates related to immunomodulatory effect is crucial for promoting innovation in biomedical and pharmaceutical science, leading to the discovery of new therapeutic molecules and the creation of advanced technological platforms for drug design. Understanding how the chemical structure of alkaloids influences their biological activity, as well as the identification, selection, and optimization, will improve the immunomodulatory efficacy, leading to safer and more effective drugs. These studies will improve the understanding of the biology of the immune system and expose new opportunities for potential therapeutic intervention in diseases involving inflammatory diseases.

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