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STRUCTURE-ACTIVITY RELATIONSHIPS OF BIOACTIVE COMPOUNDS FROM SRI LANKAN PLANTS: A REVIEW

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ABSTRACT

Sri Lanka, with its remarkable biodiversity and long history of traditional medicine, harbors a wealth of plant-derived chemical diversity. Numerous endemic species have yielded secondary metabolites spanning alkaloids, flavonoids, terpenoids, phenolic acids, coumarins, and other structural classes. Many of these compounds exhibit valuable pharmacological properties, including antioxidants, antimicrobial, antidiabetic, anti-inflammatory, and anticancer activities. However, only a limited number of studies have systematically probed the relationship between the chemical structure of these natural products and their biological activity, known as the structure-activity relationship (SAR). This review systematically examines available data on bioactive compounds isolated from Sri Lankan plants. It identifies tentative SAR trends: functional groups, ring systems, degree of conjugation, and lipophilicity recur as key determinants of activity. Additionally, significant research gaps are highlighted, along with strategic directions, including bioassay-guided fractionation, computational modeling, and semi-synthetic derivatization, that could transform primarily descriptive phytochemical literature into a resource for rational drug discovery.

Keywords: Structure-activity relationship, Sri Lankan medicinal plants, Bioactive compounds, Phytochemistry.

INTRODUCTION

Natural products have played anessential role in drug discovery for decades, providing many of the therapeutics in use today[1]. The structural diversity and biological complexity of plant secondary metabolites continue to offer unique scaffolds often absent from purely synthetic compound libraries[2]. Sri Lanka occupies a distinctive position within the Indo-Malayan biodiversity hotspot, harboring more than 3,500 flowering plant species, of which nearly 900 are endemic[3]. Many of these plants are used in traditional medicine systems, including Ayurvedic, Siddha, and indigenous practices, to treat a wide range of ailments, such as metabolic disorders, skin diseases, infections, and inflammation[4].

Despite this rich heritage, most ethnobotanical and phytochemical research remains descriptive mainly. Plants are typically collected for traditional uses, crude extracts are prepared, and biological screening is performed[5]. Pure compounds are isolated only occasionally, and systematic comparative studies linking chemical structure to biological activity are rare. In drug discovery and development, this gap limits understanding of which structural motifs confer potency, selectivity, or favorable pharmacokinetics, making it challenging to advance promising natural products into lead compounds, synthetic analogues, or preclinical candidates [6].

This review addresses this gap by mining the published literature on Sri Lankan plant-derived compounds, collating biochemical and pharmacological findings, and analyzing them through the lens of structure-activity relationships (SAR). The objective is to identify recurring trends, highlight promising chemical scaffolds, and outline strategic paths for natural product-based drug discovery rooted in Sri Lankan biodiversity.

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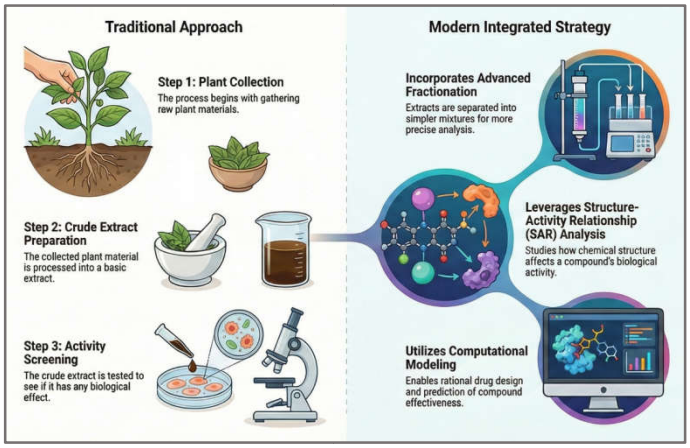

Fig. 1: Comparison between the traditional descriptive phytochemical approach and a proposed integrated strategy incorporating fractionation, structure-activity relationship analysis, and computational modeling for rational drug discovery.

Recent advances in analytical techniques, computational modeling, and molecular biology offer new avenues for systematically exploring the bioactivity of natural products. Tools such as molecular docking, quantitative structure-activity relationship (QSAR) analysis, and molecular dynamics simulations enable researchers to predict target interactions, rationalize SAR, and design optimized analogues[7]. Integrating these modern approaches with classical phytochemical studies enables a more rational exploration of the chemical diversity of Sri Lankan plants. It supports the identification of lead compounds with therapeutic potential[8].

MAJOR CLASSES OF BIOACTIVE COMPOUNDS FROM SRI LANKAN PLANTS

Alkaloids and Nitrogen-Containing Scaffolds

One of the richest sources of bioactive compounds is Sri Lanka's flora, which includes numerous alkaloid-bearing species[9].

Prominent examples include Cosciniumfenestratum, which yields the protoberberine alkaloid berberine, and Murrayakoenigii, known locally as karapincha, which produces carbazole-type alkaloids such as mahanimbine and girinimbine. In addition, several members of the Rubiaceae and Menispermaceae families remain underexplored and represent promising targets for future phytochemical investigation.

Alkaloids from these plants have shown a broad range of biological activities, including antimicrobial, antimalarial, antidiabetic, and cytotoxic/anticancer effects[10]. For instance, berberine from C. fenestratum has demonstrated antimicrobial and enzyme-inhibitory activity[11], while carbazole alkaloids from M. koenigii exhibit cytotoxicity against cancer cell lines and are reported to have antidiabetic properties[12].

From a structural perspective, several features stand out. First, planar and rigid aromatic ring systems, standard in carbazole and protoberberine alkaloids, facilitate interactions with biomolecular targets, including intercalation or stacking with DNA. Second, substitutions such as methoxy or other alkyl ether groups increase lipophilicity and may enhance membrane permeability, thereby improving cellular uptake and potency. Third, nitrogen atoms, whether in quaternary ammonium centers as in berberine or in tertiary amines, provide opportunities for ionic or hydrogen-bond interactions with enzymes or receptors. Together, these structural motifs appear instrumental in conferring bioactivity, although systematic SAR analyses remain limited.

Flavonoids, Polyphenols, and Other Phenolic Compounds

Another abundant group of natural products from Sri Lankan plants includes flavonoids, phenolic acids, tannins, and related polyphenols. Species such as Phyllanthus emblica (commonly known as nelli), Syzygium cumini, and various endemic shrubs and trees have yielded extracts with high phenolic content[13]. Extracts from some of these plants have demonstrated significant antioxidant activity and, in some cases, cytotoxicity against cancer cell lines.

Phenolic compounds are well known for their radical-scavenging activity, as hydroxyl groups on aromatic rings donate hydrogen atoms to neutralize free radicals. At the same time, conjugated systems stabilize the resulting radical species[14]. In many flavonoids, the arrangement and number of hydroxyl groups, particularly on the B-ring with 3',4' dihydroxylation, strongly influence antioxidant capacity[15]. Furthermore, glycosylation, or the attachment of sugar moieties, has often been found to reduce bioactivity, likely due to increased polarity, reduced membrane permeability, or steric hindrance[16].

In the context of cytotoxic or anticancer activity, the planarity of the flavonoid backbone and extended conjugation, such as through the C2-C3 double bond in the C-ring, may promote interactions with DNA or enzyme targets[17]. Tannins, which are larger polyphenolic molecules, introduce further complexity through their degree of polymerization, molecular weight, and cross-link patterns, all of which significantly affect their ability to penetrate cells or reach molecular targets. These considerations suggest that while phenolics are promising, their structural diversity requires careful purification and isolation for meaningful SAR analysis.

Terpenoids, Essential Oils, and Volatile Compounds

Sri Lanka is renowned for its aromatic plants: cinnamon, citronella, lemongrass, nutmeg, cloves, and many others contribute to a tradition of herbal medicine, culinary spice, and essential oil production[18]. These plants are rich in terpenoids and volatile secondary metabolites, which have been linked to antimicrobial, anti-inflammatory, antioxidant, and, in some cases, cytotoxic activities[19]. Key structural features of terpenoids that may underlie bioactivity include multiple isoprene-derived ring systems, unsaturated bonds, hydroxylation, and lipophilic side chains. For example, aromatic aldehyde groups or α, β-unsaturated aldehyde groups, such as those found in cinnamaldehyde, can act as electrophiles, reacting with nucleophilic sites on microbial proteins and thereby imparting antimicrobial properties[20]. Phenolic terpenoids, such as eugenol, combine a lipophilic aromatic skeleton with a polar hydroxyl group, enabling both membrane permeation and interactions with radicals or enzymes.

Terpenoid bioactivity is often influenced by the degree of saturation, conjugation, and substitutions such as hydroxyl, methoxy, and other oxygenated groups. Saturation, through hydrogenation, tends to reduce reactivity, whereas unsaturation and conjugation often enhance both reactivity and affinity for biological targets. Given the complexity and volatility of terpenoids, detailed SAR studies are challenging and remain rare in Sri Lankan phytochemistry. Additionally, many terpenoids are chiral molecules, yet their three-dimensional configurations, or stereochemistry, are often not reported or considered in activity studies, even though stereoisomers can differ significantly in potency or selectivity[21].

Coumarins, Quinones, and Other Mixed Scaffolds

Beyond the major classes of alkaloids, phenolics, and terpenoids, some Sri Lankan plants also produce coumarins, anthraquinones, xanthones, and other mixed or hybrid scaffolds. Although less frequently studied, these compounds exhibit a range of bioactivities, including cytotoxicity, enzyme inhibition, antimicrobial activity, and antioxidant capacity[22].

In many cases, coumarins and quinones exhibit enhanced activity when electron-withdrawing or electron-donating substituents, such as hydroxyl, carboxyl, or methoxy groups, are present, as these modulate redox behavior, binding affinity, and reactivity toward biological nucleophiles, such as thiol groups in proteins[23]. Prenylation or the addition of alkyl side chains can significantly increase lipophilicity and membrane penetration, sometimes at the expense of solubility. Xanthones with multiple hydroxylations or substitutions can combine radical-scavenging properties with cytotoxic effects, depending on their oxidation state and ring planarity[24].

RECURRING SAR THEMES: STRUCTURAL MOTIFS AND BIOACTIVITY CORRELATIONS

Functional Groups: Hydroxyls, Methoxyls, Aldehydes, Amines

Across many compound classes, functional groups are recurrent determinants of activity. Hydroxyl groups, especially in phenolics and flavonoids, consistently correlate with antioxidant and radical-scavenging activity. Their number, position, and conjugation with aromatic rings modulate redox potential and the stability of radical intermediates.

Methoxy or other alkyl ether substituents tend to increase lipophilicity, which may improve membrane permeability, a beneficial trait for cytotoxic agents or enzyme inhibitors. However, increased lipophilicity can reduce water solubility, complicating formulation or bioavailability. Electrophilic groups such as aldehydes in terpenoid-derived aromatic aldehydes or α, β-unsaturated carbonyls often confer reactivity

toward nucleophilic sites in proteins, which can contribute to antimicrobial or enzyme-inhibitory activity. Amines, whether tertiary or quaternary, in alkaloids similarly enable ionic or hydrogen-bond interactions with target macromolecules[25]. Overall, the balance between polar functional groups for binding and lipophilicity for uptake appears critical.

Ring Systems, Conjugation, and Planarity

The presence of rigid, planar aromatic rings or fused ring systems, as seen in carbazole alkaloids, protoberberines, flavonoids, xanthones, and quinones, often contributes to bioactivity. Planar structures may facilitate stacking interactions, such as intercalation into DNA, engage in π-π interactions with aromatic amino acids in proteins, or enable conjugation that stabilizes radical intermediates in antioxidants[26]. Extended conjugation, as seen in flavonoids with a C2-C3 double bond that reduces the energy gap or in quinones and xanthones, enhances electron delocalization, which can influence redox properties, radical scavenging, and reactivity. Saturation, or the loss of double bonds, tends to reduce these effects; therefore, unsaturated or conjugated systems are often more bioactive.

Lipophilicity / Hydrophobicity and Membrane Permeation

Many bioactive natural products must cross cell membranes to reach intracellular targets. Substitutions that increase hydrophobicity, such as alkyl, methoxy, prenyl, and aromatic groups, tend to facilitate membrane permeation, thereby improving potency in cell-based assays. However, excessive lipophilicity can impair solubility, reduce bioavailability, or increase non-specific binding and toxicity[27]. Thus, an optimal balance is often required, reflecting the classical "Lipinski's window" concept.

Molecular Size, Flexibility, and Polymerization

For polyphenols, tannins, and high-molecular-weight compounds, size and flexibility influence cellular uptake, distribution, and bioactivity[28]. Polymeric tannins may exhibit strong in vitro antioxidant capacity but suffer from poor cellular penetration or bioavailability. By contrast, smaller monomeric phenolics may strike a better balance between activity and pharmacokinetic properties. Flexibility, as opposed to rigid ring systems, can impair stacking interactions but may confer conformational adaptability to bind diverse targets, again underscoring the need for case-by-case SAR analysis.

REPRESENTATIVE CASE STUDIES AND SAR INSIGHTS

Alkaloid Example: Berberine from Cosciniumfenestratum

Berberine, a protoberberine alkaloid, is among the most studied compounds isolated from a Sri Lankan medicinal plant. Its planar tetracyclic structure, quaternary ammonium center, and conjugated aromatic rings make it a versatile binder, allowing interactions with nucleic acids, enzymes, and membrane components. Its broad antimicrobial spectrum and enzyme-inhibitory effects, particularly on metabolic enzymes, likely result from a combination of intercalation, ionic and hydrophobic interactions, and possibly oxidative stress induction through redox cycling.

Unfortunately, very few studies report comparative analogs, such as demethylated variants, hydrogenated cores, or side-chain modifications. The lack of semi-synthetic or synthetic derivatization, including demethylation, chain elongation, or changes in saturation, makes it difficult to assess how specific structural changes affect activity or toxicity. Such analogs would clarify the contributions of methoxy groups, rigidity, and charge distribution. Nonetheless, available data suggest that the intact protoberberine scaffold is essential, and modifications that preserve planarity and aromaticity generally retain bioactivity.

Polyphenols and Flavonoids: Antioxidant and Cytotoxic Activity in Endemic Species

In a screening of 20 endemic Sri Lankan plants against human breast cancer cell lines, such as MCF-7 and MDA-MB-231, several methanol or ethyl acetate extracts showed significant cytotoxicity, often correlating with high total phenolic and flavonoid content. These results suggest that polyphenolic compounds, including flavonoids, tannins, or phenolic acids, may be responsible for the activity[29].

Based on general flavonoid SAR from the global literature, the likely active compounds possess multiple hydroxyl groups on the B-ring, planarity through C2-C3 unsaturation, and minimal glycosylation. Polar aglycones are more readily taken up by cells. Although the original studies did not isolate individual compounds, the correlation between high phenolic content and cytotoxicity supports the hypothesis that small- to mid-sized polyphenolic aglycones with multiple free hydroxyl groups and extended aromatic systems are promising anticancer leads. However, many of these compounds may show potency in vitro but fail in vivo due to poor absorption, limited solubility, or metabolic instability.

Terpenoid / Essential Oil Compounds: Antimicrobial and Anti-inflammatory Potential

The traditional use of aromatic plants in Sri Lanka for skin diseases, inflammation, and infections suggests that their terpenoid constituents possess biological activity. For example, essential oils rich in aromatic aldehydes, such as cinnamaldehyde, or phenolic terpenoids, such as eugenol, may exert antimicrobial effects through electrophilic reactivity or membrane disruption[30].

According to general chemical principles, unsaturated or conjugated aldehydes are more reactive than saturated ones and can enable covalent modification of microbial proteins. Similarly, phenolic terpenoids benefit from a lipophilic skeleton that promotes membrane partitioning and a polar hydroxyl group that supports radical scavenging or hydrogen bonding, making them dual-function agents with both membrane-perturbing and antioxidant properties[31]. However, few modern studies have isolated pure terpenoids from Sri Lankan plants and systematically evaluated them, representing a clear opportunity for SAR investigations.

CHALLENGES, LIMITATIONS,AND RESEARCH GAPS

Phytochemical Characterization Challenges

Predominance of crude-extract studies:

Many reports screen crude extracts rather than purified compounds, making it impossible to attribute observed bioactivity to a specific molecular entity accurately and ultimately confounding SAR analysis.

Lack of purified compounds and incomplete elucidation:

Few studies isolate and fully characterize individual compounds, and when they do, yields are often low. Structural elucidation, including

Nuclear Magnetic Resonance (NMR), mass spectrometry (MS), and stereochemistry, may also be incomplete, even when bioactivity is detected.

Insufficient reporting on stereochemistry:

Many natural products, particularly terpenoids and alkaloids, are chiral. Yet their three-dimensional configuration, or stereochemistry, is often not reported or considered in activity studies, even though stereoisomers usually differ in potency or selectivity. To date, there is little published docking, QSAR, or in silico ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) modeling on Sri Lankan natural products, even though such methods can accelerate lead optimization and predict SAR.

Variability and lack of standardization:

The lack of standardization in collection and extraction protocols, including the plant part used, harvesting season, geographic origin, solvent, and extraction method, complicates comparison and reproducibility across studies. These factors strongly influence phytochemical composition and, consequently, experimental outcomes.

Structure-Activity Relationship and Drug Development Gaps

Limited SAR probing:

Only a limited number of studies have systematically examined the relationship between the chemical structure of natural products and their biological activity.

Absence of chemical modification or analog studies:

There is a lack of semi-synthetic or synthetic derivatization, such as demethylation, chain elongation, or changes in saturation. Without these analog studies, it is difficult to determine how specific structural changes affect activity or toxicity.

Minimal computational modeling:

There is little published molecular docking, QSAR, or in silico ADMET modeling of these natural products, methods that could otherwise accelerate lead optimization. To date, there is little published docking, QSAR, or in silico ADMET modeling of Sri Lankan natural products, even though such methods can accelerate lead optimization and predict SAR.

Primarily descriptive research:

The bulk of ethno botanical and phytochemical research remains primarily descriptive, and comparative studies are conducted only occasionally to relate structure to bioactivity systematically.

Pharmacokinetic Challenges

Bioavailability and solubility issues:

Many promising compounds may show potency in vitro but fail in vivo due to poor absorption, solubility, or metabolic instability. Highly lipophilic or high-molecular-weight compounds may show potency in vitro but fail in vivo for the same reasons. For instance, highly lipophilic or high-molecular-weight compounds, such as polymeric tannins, may exhibit strong in vitro antioxidant capacity but suffer from poor cellular penetration or bioavailability.

OPPORTUNITIES AND STRATEGIC DIRECTIONS FOR FUTURE RESEARCH

Bioassay-Guided Fractionation and Purification

Rather than screening crude extracts, future studies should adopt bioassay-guided fractionation workflows. Extracts should be fractionated, each fraction tested, active peaks isolated, and pure compounds fully characterized, including one- and two-dimensional NMR, mass spectrometry, and stereochemical analysis. This approach would enable an unambiguous linkage between a chemical entity and its biological activity, representing the first step toward meaningful SAR studies.

Semi-synthetic Derivatization and Scaffold Optimization

Once pure compounds are obtained, semi-synthetic modifications such as methylation or demethylation, alkylation, saturation or desaturation of double bonds, and the addition or removal of functional groups can be used to systematically probe how structural changes affect bioactivity, toxicity, and pharmacokinetics. Such efforts can transform a natural product from a laboratory curiosity into a lead-like structure amenable to optimization.

Computational Chemistry: Docking, QSAR, ADMET Prediction

A promising approach is to apply in silico methods such as molecular docking, molecular dynamics, QSAR, and ADMET modeling to known natural compounds from Sri Lanka. These methods can predict binding modes, pharmacophore features, metabolic liabilities, and drug-likeness, thereby helping to prioritize compounds or derivatives for synthesis and experimental evaluation.

Focus on Underexplored and Endemic Species, Including Marine Sources

Many endemic Sri Lankan plants remain chemically unexplored. In addition, marine flora and fauna, including algae, sea grasses, sponges, and corals, represent a largely untapped resource that may yield unique chemical scaffolds such as halogenated terpenes, novel alkaloids, and polyketides. Systematic bioprospecting combined with modern chemical analysis could substantially expand the chemical space available for SAR studies.

Standardization of Collection and Extraction Protocols

Ensuring reproducibility and comparability across studies requires the development of standardized protocols for collecting plant material, including documentation of species, locality, and season; preparing extracts with specified solvents and methods; and reporting chemical and biological data, such as yields, purity, assay conditions, and controls. Establishing these standards will enhance the reliability and value of subsequent SAR analyses.

Data Sharing and a Centralized Sri Lankan Natural Product Database

Creating a publicly accessible database of Sri Lankan plant-derived compounds with structural data (e.g., SMILES and InChI), spectral data (e.g., NMR and MS), biological data (e.g., IC_{50} and MIC values), source plant and plant part, and extraction methods would be an invaluable resource. Such a database would support meta-analyses, SAR studies, and collaborative research among chemists, pharmacologists, and computational scientists.

CONCLUSION

Sri Lanka's botanical richness offers a vast, underexplored reservoir of natural compounds, many of which exhibit promising biological activity. However, most existing studies remain descriptive and focus on crude extracts or preliminary activity screening. Without systematic isolation, structural characterization, and SAR-guided analysis, the potential of these compounds to serve as lead scaffolds for therapeutic development remains largely unrealized.

By adopting a more rigorous and integrated approach that combines bioassay-guided purification, semi-synthetic modification, computational modeling, and standardized documentation, researchers can transform Sri Lankan photochemistry into a robust platform for rational drug discovery. Given the urgent global need for novel therapeutics such as antimicrobials, anticancer agents, antidiabetics, and antioxidants, such efforts are not only intellectually compelling but also societally important.

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