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Review Article

Current Status on Phytochemicals Classification, Structure-Activity Relationship, Stereochemistry and AI-Driven Applications: A Systematic Review

Mohammed Al Saiqali[1,*], Syeda Sameena Aziz[2], Atla Venkateshwar Reddy[3]

[1]Department of Research and Innovation, Anwarul Uloom College, New Mallepally, Hyderabad, Telangana, INDIA.
[2]Department of Chemistry, Anwarul Uloom College, New Mallepally, Hyderabad, Telangana, INDIA.
[3]Department of Pharmacology, Anwarul Uloom College of Pharmacy, New Mallepally, Hyderabad, Telangana, INDIA.

ABSTRACT

Phytochemicals, plant-derived bioactive compounds, offer notable health benefits and therapeutic applications. This study extensively covers phytochemicals, their classification, sources, bioactivities, and stereochemistry, categorizing them into groups like flavonoids, alkaloids, saponins, tannins, terpenoids, and lignans. Structure-Activity Relationship (SAR) studies reveal the crucial roles of specific structural features and their biological activities. The nitrogen atoms in alkaloids conjugated double bond systems in carotenoids, diverse functional groups such as Hydroxyl, carbonyl, and epoxy groups in terpenoids, hydroxyl groups in phenolic acids and flavonoids, glycosidic bonds in saponins, and the molecular architecture of lignans. These structural elements enable interactions with various biological targets, resulting in diverse pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, anticancer, cardioprotective, and other pharmacological activities. The current review highlights the significance of stereoisomerism in their bioactivities. In case of alkaloids, the spatial arrangement of the nitrogen atom plays a significant role in binding to receptors and enzymes. Whereas in carotenoids, the configuration of the conjugated double-bond system affects their antioxidant properties. The arrangement of hydroxyl groups in phenolic acids and flavonoids determines their ability to interact with their targets and exhibit antioxidant properties. The study examines the use of AI and machine learning in phytochemical research, providing insights into molecular modelling. Finally, the review offers a complete understanding of phytochemicals, their therapeutic applications and drug discovery.

Keywords: Phytochemical classification, SAR, Stereochemistry, AI-Driven drug discovery, Therapeutic potential.

Correspondence:
Dr. Mohammed Al Saiqali
Coordinator of Research and Innovation, Associate Professor of Microbiology, Anwarul Uloom College, New Mallepally, Hyderabad-500001, Telangana, INDIA.
Email: mohdalsaid11@gmail.com

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INTRODUCTION

Phytochemicals are Low-Molecular-Weight (LMW) substances that hold a diverse array of bioactive compounds produced by plants that have long captivated human interest. These natural substances, often found in fruits, vegetables, herbs, and spices, have been utilized for centuries in traditional medicine systems worldwide.[1] Estimated figures reveal that the plant kingdom comprises at least 250,000 species. Only 10% have investigated for pharmacological applications. Phytochemicals and their derived metabolites in root, leaf, flower, stem, and bark perform several pharmacological functions in human systems.[2] The precise number of phytochemicals remains unclear; however, estimates suggest that this figure surpasses 100,000 different substances.[3]

As scientific research delves deeper into the molecular mechanisms underlying the therapeutic potential of phytochemical compounds, a growing body of evidence supports their role in promoting human health and preventing chronic diseases. These compounds, ranging from flavonoids and alkaloids to terpenes, polyphenols, saponins, carotenoids, and others, exhibit a wide range of biological activities, including anti-inflammatory, antioxidant, anticancer, and antimicrobial.[4,5] It's a fact to note that the composition of food diet plays a crucial role in human health and aging. Studies have shown that the quantity and quality of nutrients consumed are essential in altering health and disease conditions.[6] In a typical human diet, approximately 1.5 g of phytochemicals are taken daily, while vegans and vegetarians may consume significantly higher amounts of secondary metabolites. Nevertheless, no standardized intake guidelines exist for phytochemicals.[7]

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Phytochemicals are classified based on their chemical structure and functional characteristics. The phytochemical groups include carotenoids present in vegetables and fruits. Out of the 700 natural carotenoids, 50 are significant in human nutrition. Beta-carotene, for instance, accounts for up to 30% of total serum carotenoids.[8] In the Western diet, the total daily intake of carotenoids is around 6 mg. Phytosterols, which are chemically similar to cholesterol, are primarily found in dried fruits, legumes (such as alfalfa, peas, beans, Navy beans, chickpeas, lima beans, green beans, lentils, peanuts, and soy), as well as in seeds and oils. The daily intake of phytosterols ranges on average from 100 to 500 mg.[9] Phytochemicals, such as alkaloids, polysaccharides, and terpenoid polyphenols, exhibit low bioavailability. Although, the daily consumption of several grams of these compounds, only a small fraction is absorbed into the bloodstream.[10]

Phenolic compounds, in particular, provide significant health benefits due to their high antioxidant capacity. These compounds are unique in that they can evade digestion in the upper digestive tract, which is absorbed into the plasma during the digestive process.[11] Saponins are surfactant compounds that interact with proteins and lipids to form complexes. They are prevalent in leguminous plants and are consumed at an average daily intake of 15 mg. Due to their low absorption rate, saponins exhibit increased activity within the intestinal tract.[9] Polyphenols encompass phenolic acids and flavonoids, with quercetin being the most prevalent flavonoid. Flavonoids exhibit many properties, including antioxidant, anti-inflammatory, analgesic, antiproliferative, anticancer, antiangiogenic, antimicrobial, and antiviral effects.[12] The polyphenol inhibits the production of Nitric Oxide (NO), a principal mediator of inflammation, as well as Interleukin-1beta (IL-1β), Tumor Necrosis Factor-alpha (TNF-α), and Prostaglandin E2 (PGE2).[13] Flavonoids are found in red wine and dark chocolate and are predominantly located in the outer layers of vegetables (such as onions, lettuce, tomatoes, asparagus, cabbage, artichokes, and celery) and fruits (including apples, grapes, citrus fruits, cranberries, strawberries, and raspberries), as well as in tea and olive oil.[14]

Isoflavones are found in soy and its derivatives. In Western diets, the intake of isoflavones is typically less than 2 mg per day, whereas vegetarian diets can provide between 15 to 40 mg per day. Sulfides encompass all organosulfur compounds found in plants, such as those in garlic, where allicin is the principal active component.[3] Monoterpenes, including menthol (from mint), caraway seeds, and citric oil, are active compounds found in herbs and spices, with an average daily intake of up to 200 mg. These compounds exhibit significant biodiversity in humans due to their liposoluble nature. Phytoestrogens mimic the effects of endogenous estrogens; the two primary groups are isoflavones and ligands, which can function as estrogens and anti-estrogens.[15] Polysaccharides exhibit anti-inflammatory and analgesic effects that are referred to as the reduction of reactive nitrogen species and the enhancement of antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase.[16,17] Glucosinolates found in cabbage family members contribute to the characteristic flavors of radishes, mustard, and broccoli. For vegetarians and vegans people, the daily intake of glucosinolates can be twice the typical range of 10 to 50 mg.[18]

While phytochemicals' therapeutic potential is undeniable, a comprehensive understanding of the structure-activity relationships governing their biological activities remains elusive. A systematic review of existing SAR studies on phytochemicals can provide a valuable resource for researchers and the pharmaceutical industry. This review not only consolidates existing knowledge on phytochemicals but also systematically identifies critical gaps in current research, particularly in Structure-Activity Relationship (SAR) studies. By bridging these knowledge voids, it aims to establish a robust foundation for the rational design and development of innovative phytochemical-based therapies. This forward-looking approach seeks to harness cutting-edge methodologies, including AI-driven insights, to enhance SAR predictions, accelerate drug discovery, and optimize therapeutic potential-setting a new paradigm in phytochemical research. A fundamental principle in medicinal chemistry is the Structure-Activity Relationship (SAR), which explores the correlation between a molecule's chemical structure and its biological activity. By systematically modifying a compound's structure and observing the resulting changes in activity, researchers can gain insights into the molecular determinants of biological potency.[19] SAR studies have been instrumental in the development of numerous drugs, from small-molecule therapeutics to biologics. SAR analysis helps identify the molecular frameworks responsible for these compounds' bioactivity and informs the design of more potent and selective drug candidates. Understanding the key structural features that contribute to these activities is crucial for designing novel therapeutic agents and optimizing existing ones.

The biological activity of a phytochemical is linked to its chemical structure. Key structural features, such as functional groups, ring systems, and stereochemistry, influence their interactions with biological targets and their pharmacological effects.[20] Where in the case of ring systems, aromatic Rings contribute to the stability and reactivity of phytochemicals. It can participate in electron delocalization, influencing their redox properties and interactions with biological targets. In the case of Heterocyclic Rings, they contain atoms other than carbon, such as nitrogen, oxygen, or sulfur, which can introduce additional functional groups and influence the molecule's polarity and hydrogen bonding capabilities.[21]

In Stereochemistry, chirality is the spatial arrangement of atoms in a molecule that can significantly impact its biological activity. Enantiomers, molecules that are mirror images of each other, often exhibit different properties.[22] On the other hand, pharmacophore

comprises spatial features that are crucial for a molecule to interact with a particular biological target and induce a desired biological response. By identifying the pharmacophore of phytochemicals, researchers can gain insights into their mechanisms of action and design novel drug candidates.[23] Hydrogen bond donors and acceptors are common pharmacophores in phytochemicals. For example, Hydroxyl Groups (-OH) can act as both hydrogen bond donors and acceptors, enabling interactions with various biological targets. In the same manner, Carbonyl groups (C=O) act as hydrogen bond acceptors, forming hydrogen bonds with amino acid residues in proteins.[24,25] Aromatic Rings participate in π-π stacking interactions, hydrophobic interactions, and hydrogen bonding, contributing to the binding affinity of phytochemicals to their targets. Methoxy groups (-OCH3) can modify the lipophilicity and electronic properties of a molecule, influencing its absorption, distribution, and metabolism.[26]

Computational and modern Artificial Intelligence (AI) tools have revolutionized the field of phytochemical research, particularly in the realm of Structure-Activity Relationship (SAR) studies. These tools offer significant advantages in accelerating drug discovery and development processes. Molecular Docking is the technique that can predict the binding mode of a ligand to a protein receptor, providing insights into the interactions between phytochemicals and their targets. Quantum Mechanics is a method that can be used to calculate the electronic properties of molecules, which can be used to predict their reactivity and binding affinity.[27-29] By addressing these challenges and leveraging advanced computational tools, researchers can further explore the therapeutic potential of phytochemicals and accelerate the development of novel drug candidates.[30]

This review will help researchers understand the chemistry and pharmacology of phytochemicals, leading to the development of novel therapeutic agents and optimize the therapeutic potential of natural products and their applications. However, further research is needed to elucidate the molecular mechanisms underlying the biological activities of phytochemicals that contribute to drug discovery.

CLASSIFICATION OF PHYTOCHEMICALS

Phytochemicals, naturally occurring bioactive compounds found in plants, play a pivotal role in health promotion, therapeutic agents and disease prevention. The phytochemicals are mainly classified into two types, Primary and Secondary metabolites. The secondary metabolites are further classified. These bioactive compounds are broadly classified into several categories, including alkaloids, phenolics, terpenoids, glycosides, saponins, lignans, steroids, carotenoids, flavonoids, and anthocyanins. Each category encompasses a wide array of compounds, each exhibiting unique bioactivities. For example, alkaloids are known for their analgesic and anti-malarial properties,[31,32] while phenolics are celebrated for their antioxidant[33] and anti-inflammatory effects.[34] Terpenoids display antimicrobial[35,36] (Table 1) and anticancer activities,[2,37] and flavonoids are renowned for their anticarcinogenic,[38] cardiovascular protective[39] and hypoglycemic properties.[40] Through their diverse bioactivities, phytochemicals contribute to the prevention and management of chronic diseases, making them crucial components of both traditional and modern medicine. This comprehensive understanding of phytochemicals underscores their potential in therapeutic applications and the importance of continued research in harnessing their full medicinal benefits.[41]

Primary Metabolites

Primary metabolites are essential compounds produced by living organisms that play a crucial role in their growth, development, and reproduction. These metabolites are involved in the primary metabolic processes such as respiration and photosynthesis, and are typically present in most cells throughout the body. Unlike secondary metabolites, primary metabolites are not involved in ecological interactions but are vital for the physiological functions of the organism.[42,43] The major differences between primary

Table 1: Key Differences between Primary and Secondary Metabolites.

Sl. No.	Feature	Primary metabolites	Secondary metabolites
1.	Role in Growth and Development	Directly involved and essential	Not directly involved, but important for survival in a specific context.
2.	Production phase	Growth phase (Trophophase)	Secondary phase (iodophase) or in response stimuli.
3.	Distribution	Ubiquitous across many species.	Often species-specific or restricted to certain groups.
4.	Amount produced	Large amounts	Small amounts.
5.	Ease of extraction	Relatively easy	Can be challenging.
6.	Primary function	Basic metabolic processes, growth, and reproduction.	Ecological interactions, defence, signalling, etc...
7.	Examples	Carbohydrates, proteins, nucleic acids, and lipids.	Phenolics, alkaloids, terpenoids, and flavonoids.

and secondary metabolites were illustrated in (Table 1). These compounds are essential for plant growth and development, and include amino acids, the building blocks of proteins, are essential for various cellular functions, with examples including glycine, alanine, and lysine. Carbohydrates provide energy and structural support to cells, exemplified by glucose, fructose, and starch. Lipids play a crucial role in energy storage and membrane structure, with triglycerides, phospholipids, and cholesterol as key examples. Vitamins, including vitamins C, D, and B12, are organic compounds required in small amounts for normal metabolism. Additionally, organic acids, such as citric acid, lactic acid, and acetic acid, are involved in various metabolic pathways. These primary metabolites are fundamental to the proper functioning and health of living organisms.[44,45]

Secondary Metabolites

These are not directly involved in plant growth and development, but they play important roles in defense against herbivores, pathogens, and environmental stresses. They are often responsible for the flavors, aromas, and colors of plants. Secondary metabolites are further classified into several classes based on their chemical structure and biosynthetic pathways. Some of the major classes include Phenolics, alkaloids, terpenoids, flavonoids and others. They serve a lead compounds for the development of new and novel drugs. They also serve as active ingredients in traditional herbal remedies. Numerous life-saving and health-improving drugs are derived from these secondary metabolites. Prominent examples include alkaloids such as morphine a potent analgesic; quinine, a prominent antimalarial drug; vincristine, an important anticancer medication. Terpenoids like artemisinin, a highly effective antimalarial drug, and paclitaxel, used in cancer chemotherapy (Figure 1B). Phenolic compounds such as salicylic acid, the precursor to aspirin, and resveratrol, known for its antioxidant properties. Further highlighting the pharmaceutical and therapeutic potential of secondary metabolites.[46]

CLASSIFICATION OF SECONDARY METABOLITE

Phenolic Compounds

Phenolic compounds (Table 2) are a diverse group of phytochemicals characterized by the presence of one or more Hydroxyl groups (-OH) attached to an aromatic ring. They are abundant in fruits, vegetables, and other plant-based foods. Biological functions of Phenolics include Antioxidants, anticancerous, cytotoxicants, antimicrobial, vasodilating, and anti-inflammatory properties. There occurrence as natural product was found to be 45%.[47,48] Phenolic Acids are widely distributed in plants, particularly in fruits and vegetables. They are further classified into Hydroxybenzoic acids (Table 2) (e.g., gallic acid, vanillic acid), Hydroxycinnamic acids (e.g., caffeic acid, ferulic acid) (Figure 1B).[49,50] Chlorogenic acid and aloin.[50,51]

Lignans

Lignans are a group of plant compounds with a chemical structure similar to estrogen. They are found in various plant foods, particularly flaxseeds, sesame seeds, and some fruits and vegetables.[51] Lignans have been studied for their potential health benefits, including antioxidant, anti-inflammatory, and anti-cancer properties. Some research suggests that lignans may help reduce the risk of certain types of cancer, especially hormone-related cancers like breast and prostate cancer.[52] They may also offer protection against cardiovascular disease by improving cholesterol levels and reducing inflammation.[53] However, more research is needed to fully understand the mechanisms and clinical benefits of lignans. These are polyphenols derived from phenylalanine. They are found in flaxseed, sesame seeds, and other plant foods (Table 2).[54]

Lariciresinol (Stilbenes)

Stilbenes are a class of natural compounds produced in response to stress, with a diverse range of potential health benefits.[55] Resveratrol, a well-known stilbene found in grapes and berries,[56,57] has been extensively studied for its antioxidant, anti-inflammatory,[58] antimutagenic[59] and anticancer properties.[60] It may help reduce the risk of heart disease, certain cancers, and neurodegenerative diseases. Another stilbene, pterostilbene is a methylated derivative of resveratrol with enhanced bioavailability and potential benefits for metabolic health, including improved insulin sensitivity and lipid profiles.[61] While research on stilbenes is promising, further studies are needed to fully understand their mechanisms of action and clinical efficacy.

Alkaloids

Alkaloids are a diverse group of nitrogen-containing compounds found in plants, fungi, and animals. They have a wide range of biological activities and have been used in medicine for centuries.[62] Some well-known alkaloids include morphine, codeine, quinine, nicotine, reserpine, and caffeine.[63,69] Morphine and codeine are powerful pain relievers derived from the opium poppy, while quinine is used to treat malaria. Caffeine, found in coffee and tea, is a stimulant that can improve alertness and cognitive function.[63] Alkaloids have also been used in the treatment of cancer,[64,65] tuberculosis and smoking,[66] Alzheimer disease,[67] antibacterial,[68] antiviral,[69,70] heart disease, diabetic[71] (Table 2), and nervous system diseases.[72] However, it is important to note that many alkaloids are potent substances and can be toxic if not used properly.

Terpenoids

Terpenoids, also known as isoprenoids, are a large and diverse class of organic compounds found in plants, animals, and microorganisms.[73] They play various roles in living organisms, including defense mechanisms, attraction of pollinators, and

Table 2: Classification of phytochemical compounds elucidating their pharmacological application and natural sources.

Sl. No.	Phyto chemical	Class	Subclass	Biological activities	Sources	References
Class I - Phytochemicals						
1.	Gallic acid	Phenolic acids	Hydroxybenzoic acid	Antioxidant, anticancer, anti-inflammatory, antimicrobial activity.	Wine, tea, grapes, walnuts, mango, strawberries and oak galls.	[48,49]
2.	Ellagic acid	Phenolic acid	Hydroxybenzoic acid	Anticancer, antioxidant, and anti-inflammatory activity.	Black, straw and cranberries, walnuts, cranberries, pecans, and pomegranate.	[48,49]
3.	Caffeic acid	Phenolic acids	Hydroxycinnamic acid	Antioxidant, anti-inflammatory, and antineoplastic activity.	Red wine, berries, apples, olives, artichokes, and pears.	[48,49]
4.	Ferulic acid	Phenolic acids	Hydroxycinnamic acid	Anticancer, anti-inflammatory, antioxidant, and activity.	Wheat, oats, rice, barley, tomatoes, spinach, broccoli, and coffee beans.	[48,49]
5.	Chloro genic acid	Phenolic acids	Hydroxybenzoic acid	Antioxidant, antidiabetic,anti-inflammatory, antibacterial, and activity.	Coffee beans, eggplant, peaches, prunes, chicory and asparagus.	[50]
6.	Aloin	Phenolic	Anthra quinone glycoside	Laxative effect, antioxidant, anti-inflammatory and antimicrobial activity.	Aloe Vera leaves.	[51]
Class II-Phytochemicals						
1.	Reserpine	Alkaloid	Indol alkaloid	Antioxidant, anticollagenas, anti-inflammatory, antiviral, antimicrobial activity.	Rauwolfia serpentine.	[58,59, 63]
2.	Morphine	Alkaloid	Opium alkaloid	Potent analgesic and treating acute and chronic.	Seeds of *Papaver somniferum*.	[58,59]
3.	Caffeine	Alkaloid	Xanthine alkaloid	Nervous system stimulant, reduce fatigue, improve cognitive performance, headache relief and respiratory stimulation.	Coffee beans (*Coffea arabica*), tea leaves (*Camellia sinensis*), and cocoa beans (*Theobroma cacao*).	[58,59]
4.	Quinine	Alkaloid	Quinoline alkaloid	Antimalarial agent and treating muscle disorders such as nocturnal leg cramps.	Derived from the bark of the *Cinchona* tree.	[59]
5.	Nicotine	Alkaloid	Pyridine-Pyrro lidine Alkaloid	A stimulant, used in smoking cessation therapies, such as nicotine replacement therapy (NRT).	Primarily in tobacco plants Also, in small amounts in tomatoes, potatoes, and eggplants.	[61]
Class III - Phytochemicals						
1.	Thymol	Terpenoids	Monoterpenes	Local anesthetic, antimicrobial, antioxidant and anti-inflammatory activity.	Thyme leaves, oregano, *Ocimum basilicum*, and *Trachyspermum ammi*.	[67,68]

Sl. No.	Phyto chemical	Class	Subclass	Biological activities	Sources	References
2.	Limonene	Terpenoids	Mono terpenes	Antibacterial, antiseptic and antitumor activity.	Oils of orange, grapefruit and lemon.	[67,68]
3.	Pinene	Terpenoids	Mono terpenes	Antimicrobial, antioxidant, Neuroprotective and anti-inflammatory activity.	Pine, Fir, Cedar, Juniper, redwood, eucalyptus, and rosemary.	[67,68]
4.	Bisabolol	Terpenoids	Mono cyclic Sesquiterpenes	Antioxidant, antimicrobial, anti-inflammatory, antitumor and cardio protective activity.	Essential oils of *Matricaria recutita* and Candeia tree.	[67,68]
5.	Friedelin	Terpenoids	Triterpenes	wound healing, hemorrhage, itching, ulcers, Indigestion, rheumatic pain and asthma.	Phalwara butter, Indian butter tree, Diploknema butyracea / Chuiri ghee.	[67,68]
6.	Chama zulene	Terpenoids	Sesquiterpenes	Antioxidant, anti-inflammatory and antibacterial activity.	Essential oils, chamomile, yarrow and wormwood.	[68,69]
7.	Carvacrol	Terpenoids	Diterpenes	Antimicrobial, anti-inflammation, anticancer and Neuroprotective activity.	Oregano, thyme, pepperwort, and wild bergamot.	[68,69]
8.	Taxol	Terpenoids	Diterpenes	Anticancer and enhance apoptosis.	The bark of *Taxusbrevi folia*.	[70]
9.	Forskolin	Terpenoids	Diterpenes	Antibacterial and anti-inflammatory activity.	Roots of Indian Coleus plant.	[71]
10.	Arte misinin	Terpenoids	Sesquiterpenes	Antimalarial and antiviral activity.	Wormwood tree and *Artemisia annua*.	[72]
Subclass V – Flavonoids phytochemicals – Subclass I						
1.	Quercetin	Flavonoid	flavonols	Antioxidant, anti-inflammatory, antibacterial, antiviral, Neuroprotective, Cardioprotective, anticancer, antidiabetic and gastroprotective.	Citrus fruits, apples, onions, parsley, sage, tea, and red wine.	[73-78]
2.	Kaem pferol	Flavonoid	flavonols	Antioxidant, anti-inflammatory, antimicrobial, analgesic, antiallergic and antiprotozoal activity.	Apples, grapes, green vegetables, onions leaves, *Moringa olifera*.	[73-78]
3.	Myricetin	Flavonoid	flavonols	Antioxidant, anticancer, antidiabetic, anti-inflammatory and anti-amyloidogenic activity.	Grapes, Jambolan fruit and berries.	[73-78]
4.	Galangin	Flavonoid	flavonols	Antioxidant, anti-inflammatory, antiviral and antimicrobial activity.	*Alpinia officinarum, Helichrysum aureonitens,* Honey and Propolis.	[73-78]
5.	Iso rhamnetin	Flavonoid	flavonols	Antioxidant, anti-inflammatory, Antitumor activity.	Red wine, fruits, tea and vegetables.	[73-78]

Sl. No.	Phyto chemical	Class	Subclass	Biological activities	Sources	References
6.	Rhamnetin	Flavonoid	flavonols	Antioxidant, anticancer, anti-inflammatory, antiviral and antibacterial activity.	Cloves, O. falcate, Camellia sinensis, and *Ammannia multiflora*.	[73-78]
7.	Tama rixetin	Flavonoid	flavonols	Antimicrobial, Antioxidant, Cardioprotective, antirenal toxicity, Anti-inflammatory activity.	*Cyperus teneriffae, Cyperus teneriffae, Alhagi graecorum* and *Artemisia annua*.	[73-78]
8.	Icarin	Flavonoid	flavonols	Osteoporosis, Anti-inflammatory, Anticancer, Lowering Lipid, Antimetastatic, Antiatherosclerotic and Antialzheimer activity.	Dried stems and leaves of the epimedium plant, Chinese medicinal herbs.	[73-78]
9.	Morin	Flavonoid	flavonols	Cardiovascular diseases, antioxidant, anti-inflammatory, Anticancer, Antidiabetic, Antihypertensive, Antimicrobial, Cardioprotective and Antitumor activity.	*Chlorophora tinctoria, Castanea sativa, Artocarpus heterophyllus*, red wine, tea, seaweed, coffee, Guava and cereal grains.	[73-78]
10.	Fisetin	Flavonoid	flavonols	Inhibits α-amylase, Scavenges radicals.	Strawberry, apple, grape, persimmon, onion, and cucumber.	[73-78]
11.	Azaleatin	Flavonoid	flavonols	Antitumor, Antibiofilm, Wound healing and anti-dengue NS2B-NS3 protease.	Rhododendron, plumbago, carya Ceratostigma and Eucryphia.	[73-78]
12.	Gossipetin	Flavonoid	flavonols	Antioxidant, anti-inflammatory, anticancer and Neuroprotective activity.	Straw berries, apples, grapes, cucumber and onion.	[73-78]
13.	Taxifolin	Flavonoid	flavonols	Cardioprotective, Hepatoprotective, Neuroprotective, anticancer and UV protection.	Rice bran, Onion, Vinegar, Conifers and grapes.	[73-78]
Subclass II - Flavones						
1.	Luteolin	Flavonoid	Flavones	Antioxidant, anxiolytic, antidepressant, anti-aging and Cardioprotective activity.	Fruits, vegetables, flowers, herbs and *Salvia tomentosa*.	[73-78]
2.	Apigenin	Flavonoid	Flavones	Antidiabetic, cancer, antitumor, cardiovascular protective, antiviral and antibacterial activity.	Parsley, chamomile, celery, vine, spinach, artichokes and oregano.	[73-78]
3.	Chrycin	Flavonoid	Flavones	Treatment of non-alcoholic fatty liver disease. Antioxidant, anticancer, antiviral, antiallergic, neuroprotective and antibacterial activity.	Honey, propolis, passion flowers, *Passiflora caerulea, Passiflora incarnata*, and *Oroxylum indicum*.	[73-78]

Sl. No.	Phyto chemical	Class	Subclass	Biological activities	Sources	References
4.	Baicalein	Flavonoid	Flavones	Antiviral, antioxidative, anti-inflammatory, antithrombotic, and anticancer activity.	*Oroxylum indicum* and*Scutellaria lateriflora.*	[73-78]
5.	Diosmetin	Flavonoid	Flavones	Antioxidant, anti-inflammatory, anti-allergic, antibacterial, cytotoxic, antiviral antitumoural, Hepatoprotective and antithrombotic activity.	Fruits, vegetables, wines, tea and cocoa.	[73-78]
6.	Acacetin	Flavonoid	Flavones	Anticancer, anti-inflammation, antivirus, antiobesity, and antioxidant activity.	Safflower seeds, Black locust, Cirsium, Artemisia and Damiana.	[73-78]
7.	Eupatorin	Flavonoid	Flavones	Cytotoxicity, anti-inflammatory anticancer, and vasodilating activity.	*Orthosiphon stamineus, Lantana montevidensis* and *Salvia plebeian.*	[73-78]
8.	Jaceosidin	Flavonoid	Flavones	Anti-inflammatory, antioxidant, antibacterial, antiallergic and anticancer activity.	*Artemisia princeps, Salvia tomentosa* and *Artemisia vestita.*	[73-78]
9.	Pectolinarigenin	Flavonoid	Flavones	Antioxidant, anti-inflammatory, antiallergic anticancer and antitumor activity.	*Linaria vulgaris, Cirsium setidens*, Citrus fruits and *Cirsium japonicum.*	[73-78]
10.	Xanthomicrol	Flavonoid	Flavones	Antioxidant, anti-inflammatory, anticancer, antibacterial activity.	Siparuna, *Clinopodium douglasii, Achillea erba-rotta* and moschata.	[73-78]
Subclass III - Flavanols						
1.	Catechin	Flavonoid	Flavanols	Antiatherosclerosis, antihyperglycemia, antihypercholesterolemia and antiobesity.	Chocolate, red wine, green tea, fruits, vegetables and broad beans.	[73-78]
2.	Epi catechin	Flavonoid	Flavanols	Antioxidant, antimicrobial, anti-inflammatory, antitumor and cardioprotective activity.	Tea, apples, berries and cocoa.	[73-78]
3.	Gallo catechin	Flavonoid	Flavanols	Antioxidant, anticancer, anti-inflammatory, antiviral and antibacterial activity.	Tea, berries, fruits, and herbs.	[73-78]
4.	Thea flavine	Flavonoid	Flavanols	Antioxidant, anticancer activities and thearubigins of black tea.	Black tea and green tea.	[73-78]
5.	Thea rubigins	Flavonoid	Flavanols	Antioxidant, anticancer, anti-inflammatory, antiviral and antibacterial activity.	Black tea and oolong tea.	[73-78]
6.	Afzelechn	Flavonoid	Flavanols	Anti-inflammatory, antiallergic and antitumour activity.	Hazelnuts, ferns, and *Celastrus orbiculatus* herb.	[73-78]

Sl. No.	Phyto chemical	Class	Subclass	Biological activities	Sources	References
7.	Mesquitol	Flavonoid	Flavanols	Antioxidant activity.	*Prosopis juliflora.*	[73-78]
	Subclass IV - Isoflavonones					
8.	Eridictyol	Flavonoid	Flavanones	Anti-inflammatory, antioxidant, antibacterial, antiallergic and anticancer activity.	Citrus fruits, vegetables, medicinal plants and *Eriodictyon californicum*.	[73-78]
9.	Homo oeriodicty	Flavonoid	Flavanones	Anticancer, anti-inflammation, antivirus and antioxidant activity.	*Eriodictyon californicum.*	[73-78]
Subclass V - Isoflavones phytochemicals						
1.	Genistein	Flavonoid	Isoflavones	Antioxidant, anti-inflammatory, antiamyloid β and autophagy promoter.	Soybeans and soy derived foods.	[73-78]
2.	Daidzein	Flavonoid	Isoflavones	Anticancer, antioxidant, anti-inflammatory, antiviral and antibacterial activity.	Soy milk, tofu, legumes, edamame, fruits and grains.	[73-78]
3.	Glycitin	Flavonoid	Isoflavones	Anticancer, anti-inflammation, antivirus, antiobesity and antioxidation.	Soy products, tofu, soymilk, and soy sauce.	[73-78]
4.	Biochanin	Flavonoid	Isoflavones	Neuroprotective, anticancer, antioxidant, anti-inflammatory, osteogenic, antihyperglycemic activity.	Chickpea, red clover, peanuts, Alfalfa, soybean and astragalus.	[73-78]
5.	Formo nonetin	Flavonoid	Isoflavones	Antioxidant, anticancer, anti-inflammatory, antitumor and neuroprotective activity.	Legumes, red clovers (*Trifolium pratense* L.) and Chinese herb *Astragalus mmbranaceus.*	[73-78]
Subclass VI - Anthocyanins phytochemicals						
1.	Delph inidin	Flavonoid	Antho cyanins	Anti-inflammatory, antioxidant, anticancer, antiproliferative, proapoptotic, antiangiogenic and Cardioprotective activity.	Blueberries, blackberries, eggplant, red cabbage, pomegranate and dark grapes.	[73-78]
2.	Callis tephin	Flavonoid	Antho cyanins	Anti-amyloid angiopathy, antioxidant, anti-inflammatory antiviral, and cytotoxicity activity.	Pomegranate, strawberries, purple corn, *Cabernet Sauvignon, Rubus cuneifolius* and wine grapes.	[73-78]
3.	Cyanidin	Flavonoid	Antho cyanins	Antioxidant and radical-scavenging activity.	Red berries, apples, plums, red cabbage, and red onions.	[73-78]
4.	Cyanin	Flavonoid	Antho cyanins	Antioxidant and radical scavenging activity.	Red berries, apples, plums, red cabbage, and red onions.	[73-78]

Sl. No.	Phyto chemical	Class	Subclass	Biological activities	Sources	References
5.	Petunidin	Flavonoid	Antho cyanins	Antioxidant, anticancer, antimicrobial, anti-inflammatory and cardioprotective activity.	Blackcurrants, eggplants, purple sweet potatoes, red grapes and berries.	[73-78]
Class V - Phytochemical						
1.	Beta carotene	Isoprenoids	Carotenoid	Antioxidant, treating chronic diseases, vitamin A deficiency, retina, and, skin protection.	Carrots, sweet potatoes, spinach, mango, tomatoes cantaloupe, and broccoli.	[79]
2.	Lycopene	Isoprenoids	Carotenoid	Antiparasitic, antioxidant, anti-inflammatory activity.	Tomato powder, tomato paste and sun-dried tomatoes.	[80]
3.	Xantho phil	Isoprenoids	Carotenoid	Antiallergic, anticancer, and antiobese activity.	Green leafy vegetables, corn, peppers, pumpkins and papayas.	[81]
4.	Lutein	Isoprenoids	Carotenoid	Antioxidant, anti-inflammatory, cognitive activity and cardiovascular protective.	Dark green leafy vegetables like spinach, kale, broccoli and egg yolks.	[82]
5.	Zea xanthin	Isoprenoids	Carotenoid	Photoprotectant, antioxidant and reducing the risk of age-related macular degeneration.	Spinach, kale, and collard greens, corn, orange peppers and egg yolks.	[83]

protection from UV radiation. Many terpenoids possess significant medicinal properties.[74] For instance, terpenes like menthol and camphor are used in topical pain relievers and respiratory medications. Additionally, terpenoids have been studied for their potential to treat cancer, Alzheimer's disease, and other chronic conditions.[75] Terpenoids exhibit a wide spectrum of biological activities, including antimicrobial, anticancer, antihyperlipidemic, antihyperglycemic, anti-inflammatory, antioxidant, anti-parasitic, immunomodulatory, and anticholinesterase effects (Table 2). A notable example is paclitaxel,[76] a well-established terpene-based chemotherapy drug widely used in cancer treatment.[77] Similarly, artemisinin (Table 2) is derived from sweet wormwood (*Artemisia annua*), is a potent antimalarial agent with a long history of use.[78]

Flavonoids

Flavonoids are a class of polyphenolic secondary metabolites found in various fruits, vegetables, teas, and other plant products. One of the largest and most studied groups of phenolic compounds. They are known for their potent antioxidant and anti-inflammatory properties, which contribute to their health benefits, including reducing the risk of heart disease, diabetes, and certain cancers. Flavonoids are categorized into several subclasses, such as flavonols, flavanones, flavones, isoflavones, and anthocyanins, each with unique structures and functions. These compounds help regulate cellular activity, protect against oxidative stress, and support overall health. They are further classified into various subgroups, including Flavonols (e.g., quercetin (Figure 1A), kaempferol (Figure 1A), Flavones (e.g., luteolin, apigenin), Flavanones (Table 2) (e.g., hesperetin, naringenin), Isoflavones (e.g., genistein, daidzein), Anthocyanins (e.g., cyanidin, pelargonidin).[79-81]

Carotenoids

Carotenoids, called tetraterpenoid pigments, are a class of naturally occurring isoprenoids synthesized by plants and algae. They are essential for photoprotection and human health. Structurally, they are divided into carotenes, which are purely hydrocarbon-based, and xanthophylls, which contain oxygen functional groups. Among the biologically significant carotenoids, β-Carotene, xanthophylls like lutein and zeaxanthin, and lycopene play crucial roles in various physiological processes. β-Carotene, a precursor to vitamin A (retinol), is involved in vision, immune modulation, and epithelial integrity, exhibiting robust antioxidant properties that mitigate oxidative stress-induced cellular damage.[82] Lycopene, a hydrocarbon carotenoid with potent singlet oxygen-quenching capacity, is extensively studied for its role in

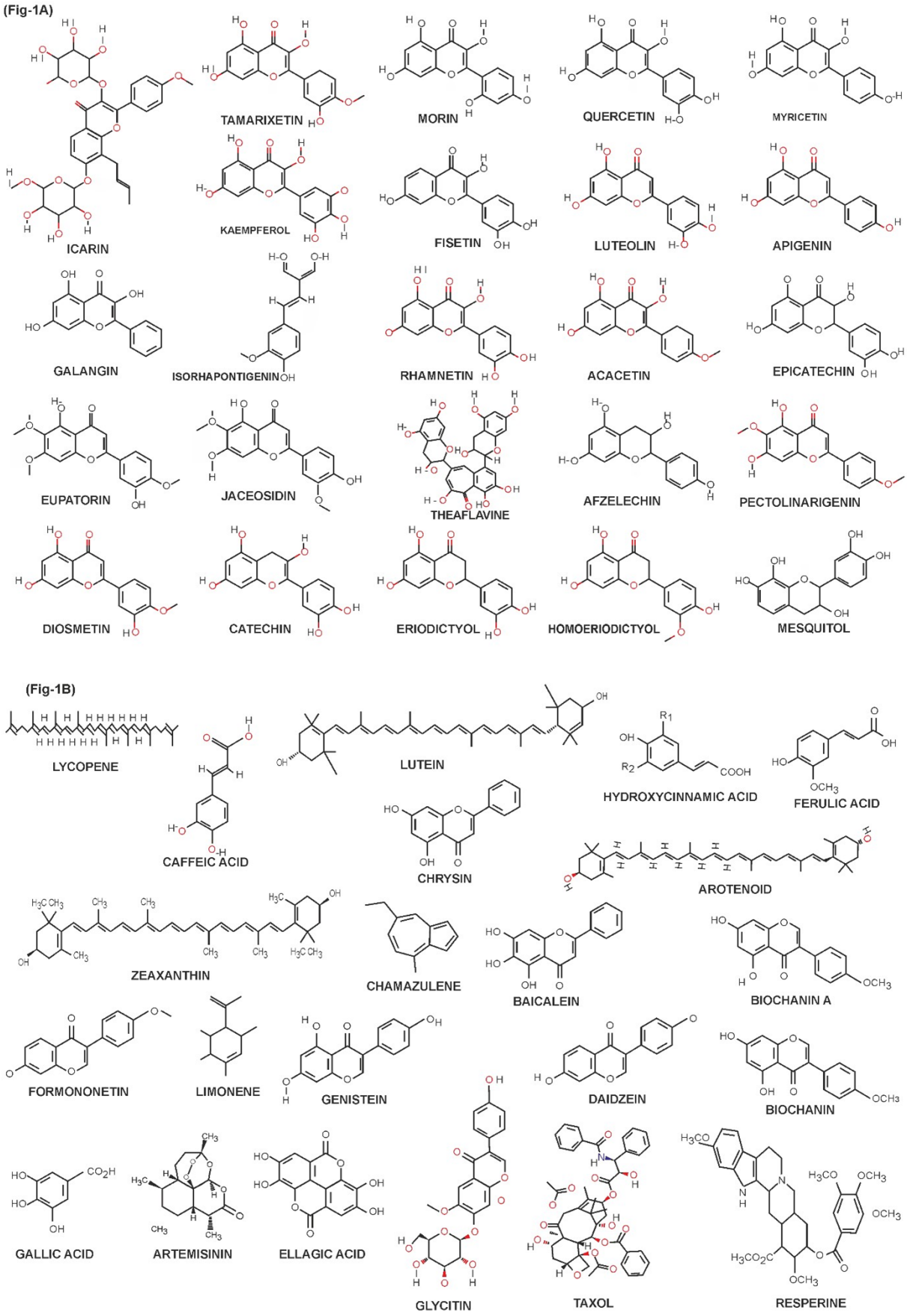


Figure 1: (1A & 1B) Structural diversity of key phytochemicals components.

reducing the risk of chronic diseases, particularly cardiovascular disorders and prostate cancer, while also serving as a protective agent against ultraviolet radiation-induced skin damage[83] (Figure 1B). Beyond ocular health, these xanthophylls such as Xanthophil demonstrate Neuroprotective and anti-inflammatory properties, contributing to cognitive preservation.[84] Lutein and zeaxanthin accumulate selectively in the macula of the retina, where they function as optical filters (Figure 1B), reducing phototoxic damage from high-energy short-wavelength light and lowering the risk of Age-related Macular Degeneration (AMD) and cataract formation.[85,86] These carotenoids are abundantly present in dietary sources such as β-Carotene-rich foods (carrots, sweet potatoes, and pumpkins), lutein- and zeaxanthin-dense sources like spinach, kale, egg yolks, and yellow-orange vegetables, and lycopene-rich foods such as tomatoes, watermelon, and pink grapefruit (Table 2). Their combined physiological functions underscore the necessity of a carotenoid-rich diet for optimal visual, neurological, cardiovascular, and dermatological health, reinforcing their significance in preventive medicine and human nutrition.

Saponins

Saponins are a diverse group of natural compounds found in various plants, including legumes, grains, and herbs. They possess a unique chemical structure that allows them to form soapy lathers when mixed with water, hence the name saponins. Beyond their foaming properties, saponins have attracted significant interest due to their potential health benefits.[84] Studies have suggested that saponins may exhibit anti-inflammatory, antioxidant, anticancer, cholesterol-lowering and triglycerides properties.[85,86] Some research indicates that they may also have potential as adjuvants in vaccines, enhancing the immune response. However, it's important to note that the specific effects of saponins can vary depending on their chemical structure and the plant source.[87] Further research is needed to fully elucidate their mechanisms of action and clinical applications.

Phytosterols

Phytosterols are plant-based compounds with a chemical structure similar to cholesterol. They are found in a variety of plant foods, including nuts, seeds, fruits, vegetables, and vegetable oils.[88] Phytosterols work by interfering with cholesterol absorption in the intestines, leading to lower levels of "bad" cholesterol in the bloodstream. This can help reduce the risk of heart disease and stroke.[89,90] While dietary intake of phytosterol-rich foods is beneficial, supplements containing concentrated phytosterols are also available. On the other hand, Phytosterols are used in the prevention of human pathologies.

STRUCTURE ACTIVITY RELATIONSHIP (SAR) STUDIES OF PHYTOCHEMICALS

Key Structural Features Influencing Biological Activity of Quercetin

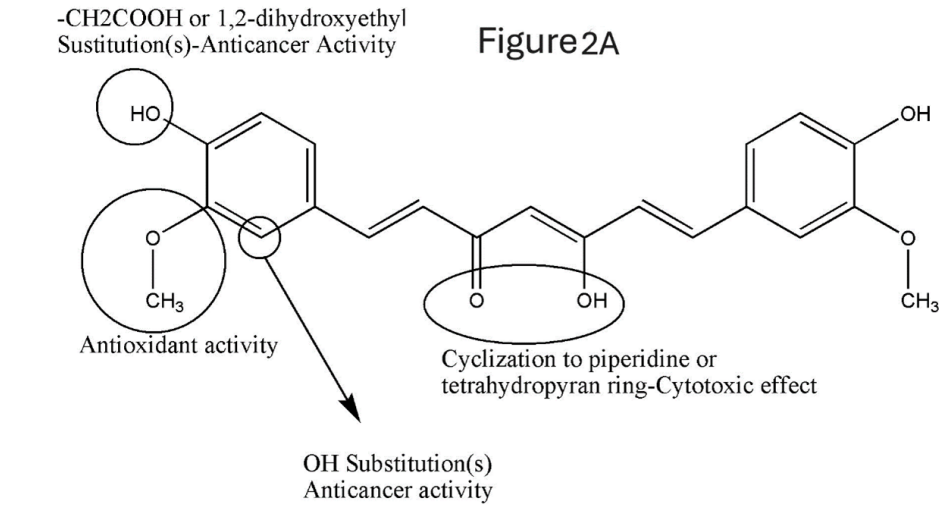
Structure Activity Relationship (SAR) studies play a pivotal role in understanding how the molecular structure of quercetin, a naturally occurring flavonoid, influences its diverse biological activities. For quercetin, SAR studies help identify which functional groups or structural features are responsible for its antioxidant, anti-inflammatory, anticancer, and other therapeutic properties.

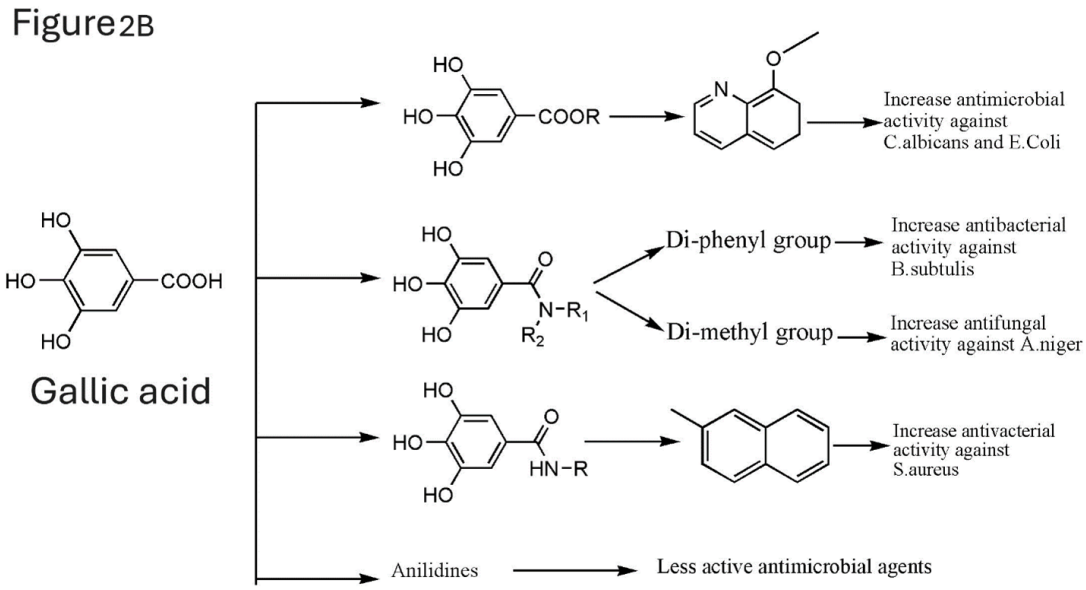
Key Structural Features of Quercetin

Quercetin has a flavonol backbone with the formula $C_{15}H_{10}O_7$. Its structure includes two aromatic rings (A and B) connected by a three-carbon bridge forming a heterocyclic ring (C). It also contains five hydroxyl (-OH) groups at positions 3, 5, 7, 3′, and 4′. These hydroxyl groups are crucial for free radical scavenging (antioxidant activity), metal ion chelation, and interaction with enzymes and receptors.[91]

Mechanism of Biological activity

It contains five hydroxyl (-OH) groups at positions 3, 5, 7, 3′, and 4′, which significantly enhance its antioxidant and anti-inflammatory properties by contributing to free radical scavenging, metal ion chelation, and modulation of oxidative stress pathways. The 3′ and 4′ hydroxyl groups in the B-ring are particularly crucial for its reactivity with Reactive Oxygen Species (ROS), making quercetin a potent antioxidant. The chromone (benzopyran) backbone of quercetin is essential for its anticancer and neuroprotective effects, as its planar structure allows it to interact with various enzymes, receptors, and signaling pathways, influencing cellular functions such as apoptosis, autophagy, and inflammation. The presence of a C2-C3 double bond in the flavone core further enhances its ability to inhibit kinases and transcription factors, making it effective in cancer therapy. Additionally, quercetin is often found in nature as glycosylated derivatives, where sugar molecules are attached to its hydroxyl groups, significantly affecting its solubility, absorption, and metabolism. For instance, quercetin-3-O-glucoside has improved bioavailability compared to its aglycone form, and the presence of sugar moieties influences its intestinal absorption and transport, impacting its therapeutic efficacy. Methoxy (-OCH3) substitutions enhance quercetin's lipophilicity, improving its cellular uptake and pharmacokinetics, allowing it to cross biological membranes more efficiently and making it more effective in targeting intracellular pathways. Methoxylated quercetin derivatives have demonstrated enhanced anti-inflammatory and anticancer properties due to better interaction with lipid bilayers. Furthermore, quercetin's hydroxyl groups enable it to chelate metal ions such as iron and copper, preventing oxidative damage caused by metal-catalyzed reactions,





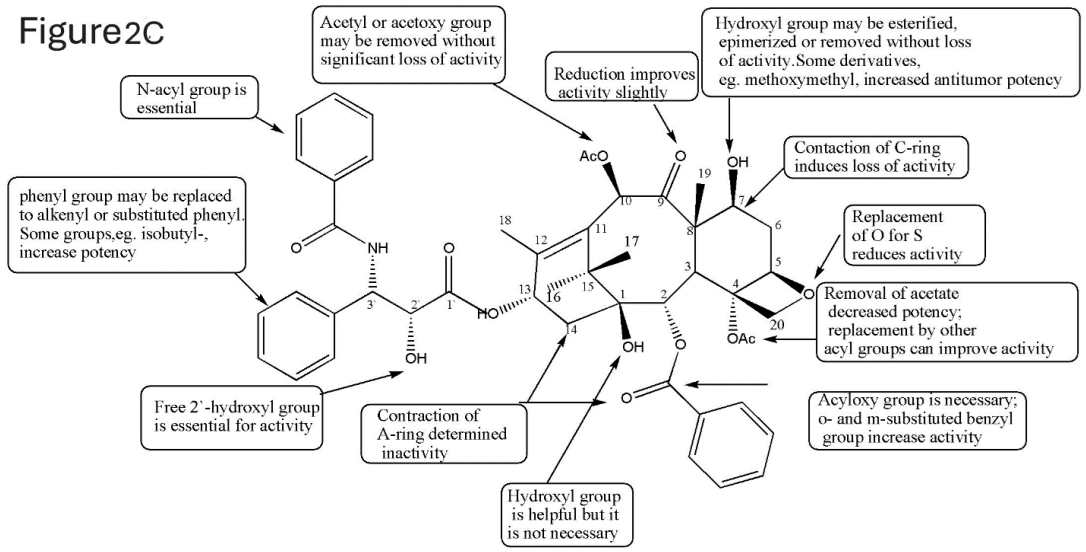


Figure 2: (2A, 2B, 2C) The structure-activity relationship plays a crucial role in defining the pharmacological efficacy of phytochemicals.

which is crucial for neuroprotection, as metal ion imbalance is linked to neurodegenerative diseases like Alzheimer's and Parkinson's. Additionally, quercetin inhibits enzymes such as Cyclooxygenase (COX) and Lipoxygenase (LOX), reducing inflammation and pain.[91,92]

It interact with various receptors and signaling pathways, influencing biological activities such as anticancer, anti-inflammatory, and neuroprotective effects. In cancer therapy, they inhibit key kinase pathways, including MAPK (Mitogen-Activated Protein Kinase), which regulates cell proliferation and survival, PI3K/Akt/mTOR, involved in cancer progression and resistance to therapy, Cyclin-Dependent Kinases (CDKs) that control cell cycle progression, and DNA-Dependent Protein Kinase (DNA-PKcs) which plays a role in DNA repair mechanisms. In inflammatory response regulation, chromone derivatives like Agar wood Chromone suppress the NF-κB signaling pathway, reducing inflammation, and modulate the Caspase pathway, which is involved in apoptosis and programmed cell death. Additionally, these compounds exhibit antioxidant and neuroprotective effects by interacting with pathways such as Nrf2, which governs antioxidant responses and protects against oxidative damage, and JNK (c-Jun N-terminal kinase), which plays a role in neuronal apoptosis and neurodegenerative conditions. These interactions highlight the therapeutic potential of chromone-based compounds in treating cancer, inflammation, and neurodegenerative disorders.[93,94]

Luteolin Structure-Activity Relationship

Luteolin, a flavonoid compound found in various fruits, vegetables, and herbs, has garnered significant attention for its diverse biological activities. Research suggests that luteolin possesses potent antioxidant, anti-inflammatory, and anticancer properties. Additionally, luteolin exhibits neuroprotective effects, potentially mitigating neurodegenerative diseases like Alzheimer's and Parkinson's. Its anti-inflammatory properties may also contribute to alleviating conditions such as arthritis and asthma and Human prostate tumour.[95]

Mechanism of Biological activity

The SAR of luteolin plays a crucial role in determining its pharmacological properties. The presence of hydroxyl groups at positions 5, 7, 3′, and 4′ enhances its antioxidant and anti-inflammatory properties, contributing to free radical scavenging and metal ion chelation, making it effective in oxidative stress-related diseases.[96]

The chromone (benzopyran) backbone is essential for its anticancer and neuroprotective effects, while its planar structure allows luteolin to interact with various enzymes and receptors, influencing cell signaling pathways. Additionally, glycosylation affects its bioavailability and pharmacokinetics, altering its absorption and metabolism, and methoxy substitutions enhance its lipophilicity, improving cellular uptake and therapeutic efficacy. The biological activities influenced by SAR include anti-inflammatory action, where luteolin inhibits the NF-κB signaling pathway, reducing inflammation, neuroprotection, where it prevents Endoplasmic Reticulum (ER) stress, making it a potential therapy for Parkinson's and Huntington's diseases, and anticancer properties, where luteolin suppresses angiogenesis and induces apoptosis, making it effective against various cancers.[97]

Structural Features Driving Naringenin Pharmacological Potential

Naringenin, a flavanone, is a bioactive compound found in citrus fruits, especially grapefruit. It exhibits various pharmacological properties, including antioxidant, anti-inflammatory, and anticancer effects. Understanding its Structure-Activity Relationship (SAR) is crucial to optimize its therapeutic potential. Naringenin, a flavonoid compound, owes its biological activity to specific structural features. The hydroxyl groups at positions 4', 5, and 7 play a crucial role in its antioxidant and anti-inflammatory properties by donating hydrogen atoms to stabilize free radicals and forming hydrogen bonds with target proteins, thereby influencing their binding affinity and biological activity. The pyran ring structure provides rigidity and planarity to the molecule, which is essential for optimal interactions with biological targets. Naringenin exists as two enantiomers, (S)-naringenin and (R)-naringenin, with the (S)-enantiomer generally exhibiting higher biological activity. Naringenin's hydroxyl groups contribute to its antioxidant properties by directly scavenging free radicals or chelating metal ions, thereby preventing oxidative stress. Additionally, naringenin's redox properties allow it to act as a reducing agent, neutralizing reactive oxygen species and further contributing to its antioxidant activity. Naringenin can inhibit breast and lung cancers through ERK1/2 and AKT/MMP pathways. Additionally, naringenin's redox properties allow it to act as a reducing agent, neutralizing reactive oxygen species. In terms of anti-inflammatory activity, naringenin can inhibit enzymes like Cyclooxygenase (COX) and Lipoxygenase (LOX), reducing the production of inflammatory mediators.[98,99]

Furthermore, it can modulate signaling pathways involved in inflammation, such as the Nuclear Factor-Kappa B (NF-κB) pathway. Beyond its antioxidant and anti-inflammatory properties, naringenin has also been shown to possess anticancer, neuroprotective, and cardiovascular health benefits. It can induce apoptosis, inhibit cell proliferation, and modulate cell cycle progression in cancer cells. Additionally, naringenin can protect neurons from oxidative damage and inflammation. In terms of cardiovascular health, it can help reduce the risk of cardiovascular diseases by lowering blood pressure and cholesterol levels.[100] Hydroxyl group modifications can significantly alter naringenin's activity and selectivity. Adding or removing hydroxyl groups, or changing their positions, can impact the compound's polarity,

hydrogen bonding capacity, and overall molecular structure, leading to changes in its biological effects. Glycosylation, the attachment of sugar moieties, can dramatically alter naringenin's physicochemical properties. It can increase its solubility, bioavailability, and stability, while also influencing its pharmacokinetic profile.[101] The type of sugar moiety and the precise position of glycosylation can modulate the compound's interaction with biological receptors and enzymes, thereby affecting its biological activity. Additionally, the stereochemistry at naringenin's chiral center can influence its biological activity, as different enantiomers may exhibit varying degrees of potency and selectivity.

Structural characteristics affecting Biological Activity of Genistein

Genistein, a phytoestrogen primarily found in soybeans and other legumes, has garnered significant attention for its diverse biological activities, including antioxidant, anti-inflammatory, and anticancer properties. Understanding its Structure-Activity Relationship (SAR) is crucial for optimizing its therapeutic potential. The hydroxyl groups at positions 4', 5, and 7 are essential for genistein's antioxidant and anti-inflammatory activities. These groups can donate hydrogen atoms to stabilize free radicals, thereby mitigating oxidative stress. Additionally, they can form hydrogen bonds with target proteins, influencing their binding affinity and biological activity. The pyran ring structure provides rigidity and planarity to the molecule, which is crucial for optimal interactions with biological targets. This structural feature contributes to genistein's ability to bind to specific receptors and enzymes, eliciting its diverse biological effects. Understanding its Structure-Activity Relationship (SAR) is crucial for optimizing its therapeutic potential. Genistein's hydroxyl groups play a pivotal role in its antioxidant activity.[102] These groups can directly donate hydrogen atoms to neutralize free radicals, mitigating oxidative stress. Additionally, genistein can chelate metal ions, preventing them from catalyzing oxidative reactions. Genistein exhibits anti-inflammatory properties by inhibiting enzymes like Cyclooxygenase (COX) and Lipoxygenase (LOX), reducing the production of inflammatory mediators. Furthermore, it can modulate signaling pathways involved in inflammation, such as the nuclear factor-kappa B (NF-κB) pathway. Beyond its antioxidant and anti-inflammatory properties, genistein has also been shown to possess anticancer, neuroprotective, and cardiovascular health benefits. It can induce apoptosis, inhibit cell proliferation, and modulate cell cycle progression in cancer cells. Additionally, genistein can protect neurons from oxidative damage and inflammation. In terms of cardiovascular health, it can help reduce the risk of cardiovascular diseases by lowering blood pressure and cholesterol levels. On the other hand, RAR can be achieved by the modification of Hydroxyl group can significantly alter genistein's activity and selectivity. Adding or removing hydroxyl groups, or changing their positions, can impact the compound's polarity, hydrogen bonding capacity, and overall molecular structure, leading to changes in its biological effects. Glycosylation, the attachment of sugar moieties, can dramatically alter genistein's physicochemical properties.[103,104] It can increase its solubility, bioavailability, and stability, while also influencing its pharmacokinetic profile. The type of sugar moiety and the precise position of glycosylation can modulate the compound's interaction with biological receptors and enzymes, thereby affecting its biological activity.

Structural Perspective on Curcumin Biological Activity

Curcumin, a natural polyphenol derived from turmeric, possesses potent anti-inflammatory, antioxidant, and anticancer properties. However, its limited bioavailability and rapid metabolism hinder its therapeutic potential. To address these challenges, researchers have synthesized and evaluated various curcumin derivatives. Structure-Activity Relationship (SAR) studies have revealed key structural features influencing curcumin's biological activity. Modifications to the aliphatic chain, aromatic rings, ketone groups, and conjugate additions have been explored. Lengthening or shortening the aliphatic chain can affect potency and bioavailability, as exemplified by C-5 and C-6 analogs with improved anticancer activity. Substitutions on the aromatic rings, such as methoxy, hydroxy, and fluoro groups, enhance antioxidant activity, as demonstrated by 4-methoxy curcumin's increased antiproliferative effect.[105] Replacing the ketone groups with hydroxyl, methoxy, or alkyl groups can alter biological activity and stability, with reduced ketone groups leading to improved stability. Conjugate additions of fatty acids, amino acids, or sugars can enhance bioavailability, as illustrated by the curcumin-piperine conjugate, which improves cognitive function. Key findings from these studies include increased potency through modifications at C-4, C-5, and C-6 positions, improved stability via reduced ketone groups and conjugate additions, and enhanced antioxidant activity through aromatic ring substitutions and aliphatic chain modifications, and selective targeting of cancer cells by derivatives with specific functional groups (Figure 2A).[106,107] Promising curcumin derivatives include Demethoxycurcumin (DMC), Bisdemethoxycurcumin (BDMC), curcumin-piperine conjugate, and Tetrahydrocurcumin (THC), which offer potential advantages over natural curcumin in terms of potency, stability, bioavailability, and targeted therapeutic effects.[108]

Structural Determinants of Cyanidin's Biological Activity

Cyanidin, an anthocyanidin pigment found in various red, purple, and blue fruits and vegetables, exhibits potent antioxidant, anti-inflammatory, and anticancer properties. Its Structure-Activity Relationship (SAR) is pivotal in optimizing its therapeutic potential. The hydroxyl groups at positions 3, 5,

7, 3', and 4' are crucial for its antioxidant and anti-inflammatory activities, as they can donate hydrogen atoms to stabilize free radicals and form hydrogen bonds with target proteins.[109] The flavylium cation structure contributes to its color, stability, and antioxidant activity by facilitating electron transfer. Cyanidin's antioxidant activity involves direct radical scavenging through hydroxyl group hydrogen donation and metal chelation to prevent oxidative reactions. It exhibits anti-inflammatory effects by inhibiting enzymes like COX and LOX, modulating signaling pathways like NF-κB, and inducing apoptosis, inhibiting cell proliferation, and modulating cell cycle progression in cancer cells. Additionally, cyanidin offers neuroprotective benefits, protects against cardiovascular diseases, and its biological activity can be influenced by hydroxyl group modifications and glycosylation, which affect solubility, bioavailability, stability, and target interactions.[110]

Influential Structural Elements of Gallic acid Biological Function

Gallic acid, a polyphenol belonging to the hydroxybenzoic acid family, possesses diverse biological activities including antioxidant, anti-inflammatory, and antimicrobial properties. Its Structure-Activity Relationship (SAR) is intricate, influenced by several factors. The presence and position of multiple hydroxyl groups on the aromatic ring, particularly the 3,4,5-trihydroxy configuration, are crucial for its antioxidant activity and hydrogen bonding capabilities. The planar aromatic ring, essential for electron delocalization and radical stabilization, benefits from electron-donating groups like hydroxyl. The carboxylic acid group, capable of ionization and metal chelation, affects solubility and biological interactions. SAR studies on gallic acid derivatives have shown that methylation can reduce antioxidant activity but improve lipophilicity, while glycosylation enhances water solubility and stability but may decrease antioxidant activity (Figure 2B). Esterification can modulate lipophilicity, solubility, and biological activity. The antifungal activity of synthesized compounds against *Aspergillus niger* revealed that 3,4,5-trihydroxy-N,N-dimethylbenzamide exhibited the highest potency. However, an increase in carbon chain length resulted in a decline in activity, as demonstrated by the reduced efficacy of 3,4,5-trihydroxy-N,N-diethylbenzamide. Regarding the antibacterial activity of gallic acid derivatives against *Bacillus subtilis*, 3,4,5-trihydroxy-N,N-diphenylbenzamide and 3,4,5-trihydroxy-N-(naphthalen-2-yl)benzamide were identified as the most potent antibacterial agents. Their enhanced activity is attributed to the presence of bulky aromatic groups, such as two phenyl substituents and a bicyclic naphthalene ring, suggesting that amide derivatives with substantial aromatic moieties exhibit superior antibacterial efficacy. Furthermore, the formation of anilides does not enhance the antimicrobial profile of 2-amino benzoic acid, as none of the synthesized anilide derivatives demonstrated significant activity.[111-113]

Critical SAR Attributes Affecting Lignans Bioactivity

Structure–Activity Relationship (SAR) studies play a crucial role in understanding how the chemical structure of lignans influences their biological activity. Lignans are a class of polyphenolic compounds known for their antioxidant, anticancer, anti-inflammatory, and neuroprotective effects. Here's how SAR impacts their bioactivity, with a focus on mechanisms of action includes:

Key SAR Features Influencing Lignans Bioactivity

Substitution patterns on aromatic rings

Hydroxyl, methoxy, and other substituents on the aromatic rings significantly affect antioxidant and estrogenic activity. For example, hydroxyl groups enhance radical scavenging, while methoxy groups can modulate estrogen receptor binding.[114]

Stereochemistry and configuration

The spatial arrangement of atoms (e.g., cis/trans isomerism) influences how lignans interact with biological targets like enzymes or receptors. Certain stereoisomers show stronger anticancer or anti-inflammatory effects.

Linkage type and position

The type of bond connecting the two phenylpropanoid units (e.g., β–β′, β–O–4′) affects metabolic stability and receptor affinity. For instance, dibenzylbutyrolactone lignans often show potent cytotoxicity due to their stable lactone ring.

Functional Groups

The presence of lactone, furan, or tetrahydrofuran rings can enhance bioavailability and target specificity. These groups often contribute to the compound's ability to inhibit enzymes or modulate signaling pathways.

Key Features Driving Stilbenes Biological Activity

Stilbenes, a class of natural compounds, possess a diverse range of biological activities including antioxidant, anti-inflammatory, and anticancer properties. Their Structure-Activity Relationship (SAR) is intricate and influenced by several key structural features. The central trans-stilbene backbone is essential for their biological activity, while the number and position of hydroxyl groups significantly impact their antioxidant and other biological activities. Additionally, other functional groups such as methoxy, methylenedioxy, and halogen groups can modulate their activity. Hydrogen bonding, electron-donating groups, planarity, and lipophilicity further contribute to their biological activity. Numerous SAR studies have revealed that the number and position of hydroxyl groups significantly impact antioxidant activity, while the stereochemistry of the stilbene backbone influences receptor binding affinity. Moreover, the presence of additional functional groups like methoxy and methylenedioxy

groups can modulate activity, and the molecule's conformation can affect its interaction with biological targets.[114,115]

Mechanisms of action

Lignans exhibit their bioactivity through several mechanisms of action. For antioxidant activity, they activate the Nrf2 signaling pathway, which upregulates cytoprotective genes and combats oxidative stress. In terms of anticancer effects, lignans induce apoptosis and inhibit proliferation by modulating pathways such as PI3K/Akt, MAPK, and NF-κB. Their anti-inflammatory action involves the suppression of pro-inflammatory cytokines and enzymes like COX-2 and iNOS. Additionally, some lignans act as phytoestrogens, binding to estrogen receptors and influencing hormone-related cancers. If you're diving into drug design or phytochemical research, Structure–Activity Relationship (SAR) insights can guide the synthesis of more potent lignan derivatives.[115,116]

Deciphering the Structure-Activity Relationship in Morphine

The Structure-Activity Relationship (SAR) of morphine plays a crucial role in its bioactivity, influencing its analgesic potency, receptor binding, and pharmacokinetics. SAR studies help understand how modifications to morphine's chemical structure affect its interaction with opioid receptors and its overall therapeutic effects.

Key Aspects of SAR in Morphine

Alicyclic Ring Modifications

Changes to the hydroxyl group at C-6, such as methylation or oxidation, can enhance analgesic activity and toxicity. The C-6 hydroxyl group plays a crucial role in morphine's bioactivity, and when methylated, oxidized, or removed, the compound's lipophilicity increases, enhancing its ability to cross the blood-brain barrier. Reduction of the C-6 keto group to C-6 β-hydroxyl, as seen in oxymorphone, leads to Nalbuphine, which exhibits antagonistic effects on μ-opioid receptors. Saturation of the C-7 double bond results in dihydromorphine, which has higher potency due to improved receptor binding. Additionally, bridging of C-6 and C-14 via an ethylene linkage produces oripavines which are thousands of times more potent than morphine.[117]

Aromatic Ring Modifications

The phenolic hydroxyl group at C-3 is essential for opioid receptor binding, and substituting or removing this group reduces analgesic activity. The hydrophobic interactions between the aromatic ring and the opioid receptor pocket stabilize morphine's binding, enhancing its agonistic effects. Additionally, modifications that introduce electron-withdrawing groups can alter binding affinity, affecting potency and duration of action.[117,118]

Nitrogen Modifications

The tertiary nitrogen at C-17 is critical for receptor selectivity. N-methyl substitution enhances agonistic activity, while larger substitutions like N-phenylethyl increase potency tenfold. N-allyl and N-cycloalkyl substitutions convert morphine into opioid antagonists, useful in reversing opioid overdose. The size and polarity of the nitrogen group influence blood-brain barrier penetration, affecting onset and duration.[118]

Blood-Brain Barrier Penetration

The morphine's hydrophilic nature limits its ability to cross the Blood-Brain Barrier (BBB) efficiently. Modifications that increase lipophilicity can enhance central nervous system activity. Morphine's hydrophilic nature limits its ability to cross the Blood-Brain Barrier (BBB) efficiently. Lipophilic modifications, such as esterification, enhance BBB permeability, increasing Central Nervous System (CNS) activity. Morphine-6-Glucuronide (M6G), a metabolite, has higher BBB penetration and greater analgesic potency than morphine itself.[119,120] These SAR insights are critical for designing morphine analogs with improved efficacy and reduced side effects.

Role of Structural Features in the biological Activity of Menthol

Menthol, a cyclic mono-terpene alcohol, is well-known for its cooling sensation and various pharmacological effects. Its Structure-Activity Relationship (SAR) is complex and influenced by several structural features. The cyclohexane ring forms the core structure, while the isopropyl group at the 1-position contributes to lipophilicity and receptor binding. The hydroxyl group at the 3-position is essential for hydrogen bonding and receptor interactions. The stereochemistry of the chiral centers significantly affects the molecule's biological activity, with specific configurations like (-)-menthol and (+)-menthol influencing receptor interactions and cooling sensation. The presence and position of the hydroxyl group are crucial for hydrogen bonding and receptor activation, while the isopropyl group contributes to lipophilicity, affecting membrane permeability and receptor binding. While extensive SAR studies on menthol analogs are not as abundant as for other drug classes, research has been conducted to explore the effects of structural modifications on its properties, including hydroxyl group modification, isopropyl group modification, and ring modifications, which can alter polarity, hydrogen bonding, lipophilicity, and receptor interactions.[121-123]

Structural Insights into the Bioactivity of Camphor

Camphor, a bicyclic monoterpene ketone, possesses a unique structure that contributes to its diverse biological activities, including analgesic, anti-inflammatory, and antimicrobial properties. The bicyclic ring system provides a rigid framework, while the carbonyl group in the ketone functional group is crucial for its biological activity. Methyl groups on the ring system

influence the molecule's lipophilicity and steric properties. The stereochemistry of the chiral center significantly impacts the molecule's biological activity, and the presence and position of functional groups, such as the ketone group, can modulate activity. The conformation of the bicyclic ring system can influence receptor binding and biological activity, while lipophilicity affects its ability to cross cell membranes. While extensive SAR studies on camphor analogs are not as abundant as for other drug classes, research has been conducted to explore the effects of structural modifications, including ketone group modification, methyl group modification, and ring modifications, which can alter reactivity, hydrogen bonding, lipophilicity, steric properties, conformation, and receptor interactions.[121-123]

Key Determinants of β-carotene Biological Functions

β-Carotene, a carotenoid with a distinctive polyene structure, owes its potent antioxidant properties primarily to its conjugated double-bond system. This long chain of conjugated double bonds is responsible for strong light absorption and antioxidant activity, while the cyclic end groups contribute to the molecule's stability and overall structure.[124]

Structural Features and Their Functional Impact

β-Carotene is a C40 tetraterpenoid with a long chain of conjugated double bonds and two β-ionone rings. These features are critical for antioxidant activity: the conjugated double bonds allow β-carotene to quench singlet oxygen and neutralize free radicals, protecting cells from oxidative stress. Provitamin A function: the β-ionone rings are cleaved by β-Carotene Oxygenase 1 (BCO1) to produce retinal, which is further converted into retinoic acid, a key regulator of gene expression via nuclear Receptors (RAR and RXR).[125] Anti-inflammatory effects: SAR studies show that β-carotene modulates pathways like TNF signaling and sphingomyelin signaling, influencing cytokine production and immune responses.[124,125]

Mechanism of Action

Absorption and Metabolism: After ingestion, β-carotene is absorbed in the intestine and incorporated into micelles. It is then cleaved by BCO1 into retinal, which can be stored, oxidized, or converted into retinoic acid. Gene Regulation: Retinoic acid binds to Retinoic Acid Receptors (RARs) and Retinoid X Receptors (RXRs), modulating transcription of genes involved in cell differentiation, immune function, and vision. Network Pharmacology Insights: Recent studies using network pharmacology and molecular docking have identified over 190 β-carotene targets, linking it to pathways involved in inflammation, oxidative stress, and cancer. These include RNA polymerase II transcription, steroid hormone receptor activity, and enzyme binding.[124-126]

Structural Elements and Their Role in Zeaxanthin Bioactivity

Zeaxanthin, a xanthophyll carotenoid, is a crucial nutrient for eye health, particularly in maintaining macular pigment density. Zeaxanthin and lutein have important role in the protection against damage by intense light in both human eye[127] and plants. Its Structure-Activity Relationship (SAR) is closely tied to its unique chemical structure. Key structural features include a polyene chain of conjugated double bonds responsible for its vibrant color and antioxidant properties, two hydroxyl groups contributing to polarity and hydrogen bonding, and cyclic end groups providing structural stability. The length of the conjugation system, the number and position of hydroxyl groups, and the isomerization state of zeaxanthin influence its biological activity. While specific SAR studies on zeaxanthin analogues are limited, general research on carotenoids indicates that increasing conjugation length enhances antioxidant activity, hydroxyl groups affect polarity and solubility, and the all-trans isomer is generally more biologically active than cis-isomers.[128]

STRUCTURAL ASPECTS GOVERNING SAPONINS BIOLOGICAL EFFICACY

Saponins are amphiphilic molecules composed of a sugar moiety linked to either a triterpenoid or steroid aglycone. Their Structure-Activity Relationship (SAR) features significantly influence their biological activity. Here are some key aspects:

Aglycone Structure

Saponins are broadly classified into triterpenoid and steroidal saponins, each exhibiting distinct biological effects due to their structural differences. Triterpenoid saponins, such as oleanane, ursane, and lupane derivatives, are well-documented for their anti-inflammatory, anticancer, and immunomodulatory properties, making them valuable in pharmacological applications. In contrast, steroidal saponins, including spirostane and furostane compounds, demonstrate antifungal and antimicrobial activities, contributing to their therapeutic potential. The hydrophobic nature of the aglycone core plays a crucial role in determining the bioavailability and functional interaction of saponins with lipid membranes, directly influencing their absorption and biological efficacy. This structural specificity underscores the diverse pharmacological potential of saponins in drug development and biomedical research.[129]

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Membrane Interaction

Saponins exhibit potent cell membrane-disrupting properties due to their ability to form complexes with cholesterol, resulting in hemolytic and cytotoxic effects. This interaction alters the structural integrity of biological membranes, contributing to their diverse pharmacological applications.[131,132] Their immunomodulatory potential is harnessed in vaccine adjuvants, where they enhance immune responses by facilitating antigen uptake and stimulating immune cell activation.[133]

Additionally, the amphiphilic nature of saponins enables effective interaction with lipid bilayers, influencing cell permeability and drug delivery mechanisms. This dual functionality membrane disruption and bioavailability enhancement makes them valuable in biomedical formulations aimed at optimizing cancer therapeutic efficacy.[132]

Foaming and Surfactant Properties

Saponins exhibit soap-like behaviour with amphiphilic properties, allowing them to function as natural surfactants, which enable the formation of stable foams. This characteristic makes them highly valuable in cosmetic and pharmaceutical applications, where they contribute to the texture and efficacy of formulations.[134] Their interaction with lipid bilayers plays a crucial role in modulating cell permeability, thereby influencing drug delivery systems and enhancing the bioavailability of therapeutic compounds. Additionally, saponins serve as natural emulsifiers in food and pharmaceutical formulations, facilitating the stabilization of emulsions and improving the solubility of hydrophobic ingredients, making them essential components in diverse biomedical and industrial applications.[135]

Structural Factors Affecting Phytosterols Bioactivity

Structure-Activity Relationship (SAR) features play a crucial role in influencing the biological activity of phytosterols. These natural sterols, found in plants, have distinct structural properties that impact their physiological functions. Here are some key SAR features:

Steroid Nucleus and Side Chains

Phytosterols possess a Cyclopentanoperhydrophenanthrene (CPPPT) nucleus, similar to cholesterol, but with variations in their side chains. These differences, such as the presence of ethyl or methyl groups, impact their ability to interact with lipid membranes and enzymes. The hydrophobic nature of the side chain influences their solubility and incorporation into micelles, affecting their absorption and biological activity.[136]

Cholesterol Modulation

Phytosterols compete with cholesterol for absorption in the intestine, reducing overall cholesterol uptake. They interfere with micellar solubilization, preventing cholesterol from being efficiently absorbed. Additionally, phytosterols activate Liver X Receptors (LXR), which regulate cholesterol metabolism and promote its excretion via bile acids.[137]

Oxidation Products

Phytosterols can undergo oxidation, forming derivatives such as keto, hydroxy, and epoxy sterols. These oxidation products may have pro-inflammatory and pro-atherogenic effects, influencing lipid metabolism and cardiovascular health. However, formulation strategies, such as co-formulation with antioxidants, can help reduce oxidation and maintain their beneficial properties.[138]

Bioavailability and Absorption

Despite their cholesterol-lowering effects, phytosterols have low bioavailability (0.5-2%), meaning only a small fraction is absorbed. Their absorption is regulated by ATP-Binding Cassette (ABC) transporters, which actively pump them out of enterocytes. The formulation of phytosterols, such as emulsification or esterification, can enhance their solubility and improve absorption.[139]

The Role of Stereochemistry in Phytochemical Activity and their Therapeutic Efficacy

Stereochemistry, the study of the spatial arrangement of atoms in molecules, plays a crucial role in their biological activity. Like handedness in humans, molecules can exist as mirror images, called enantiomers, which may have different effects despite sharing the same chemical formula. The 3D structure of phytochemicals significantly influences their interaction with biological targets, affecting efficacy, potency, and toxicity. Since enzymes and receptors are highly specific in molecular recognition, the stereochemical configuration of a phytochemical determines its ability to bind to target sites and trigger desired biological responses. Understanding these nuances is essential for optimizing therapeutic potential and designing phytochemical-based drugs.[140]

Taxol (paclitaxel) is a complex molecule with multiple chiral centers, making its stereochemistry crucial to its biological activity. The stereochemistry of Taxol influences its ability to bind to microtubules, stabilizing them, and preventing their disassembly, which is essential for its anticancer effects.

Stereochemistry of Taxol

Taxol possesses 11 chiral centers, which are essential for its ability to bind to β-tubulin and stabilize microtubules (Figure 2C). These chiral centers define the three-dimensional configuration of the molecule, optimizing its interaction with the target.[141]

Key Chiral Centers and Their Role

The structural composition of Taxol significantly influences its functionality. The C-2 benzoyl group is crucial for microtubule binding and stabilization, while the C-4 acetyl group contributes to hydrogen bonding with tubulin. The C-7 hydroxyl group enhances binding affinity, and the C-9 and C-10 positions affect the rigidity of the taxane ring. Additionally, the C-13 side chain plays a pivotal role in binding specificity.[141]

Interaction with Microtubules

Taxol binds to β-tubulin at a designated site, inhibiting microtubule depolymerization. Its C-13 side chain serves a vital function in anchoring the drug to β-tubulin, ensuring a stable interaction and efficient microtubule stabilization.[142]

Mechanism of Anchoring

The C-13 side chain contains a phenylisoserine moiety, which enhances binding specificity by interacting with hydrophobic pockets within β-tubulin, thereby increasing affinity. Furthermore, the amide bond in the side chain forms hydrogen bonds with tubulin residues, stabilizing the molecular complex and ensuring the precise orientation of Taxol within the tubulin-binding site.[141,142]

Impact on Microtubule Stability

The C-13 side chain plays a crucial role in preventing microtubule depolymerization by locking tubulin in a stable conformation and contributing to lattice expansion, enhancing microtubule rigidity. The taxane ring system further stabilizes microtubules by reinforcing lattice expansion.[143]

Mechanism of Binding

The Taxane Core precisely fits into the taxane-binding site of β-tubulin, locking tubulin in a stable conformation to prevent microtubule breakdown. The C-13 side chain enhances binding affinity and ensures the correct orientation within the binding site. Hydrogen bonding and hydrophobic interactions between the Taxane Core and tubulin further strengthen the attachment.[143]

Effects on Microtubules

Taxane binding facilitates microtubule lattice expansion, increasing their rigidity. This stabilization impedes cell division, ultimately inducing apoptosis in cancer cells. Studies indicate that modifications to the Taxane Core can significantly influence binding efficiency and therapeutic efficacy.[144]

Hydrogen Bonding

Hydroxyl and acetyl functional groups contribute substantially to strong hydrogen bonding interactions with tubulin, reinforcing Taxol's binding stability and biological activity.

Impact on Biological Activity

Taxol's microtubule stabilization occurs through its interaction with β-tubulin, preventing depolymerization. This results in cell cycle arrest, particularly in the mitotic phase, preventing cancer cell proliferation. Small structural modifications in Taxol's stereochemistry can markedly alter its effectiveness.[143,144]

Effect on Activity

Taxol binds to β-tubulin in microtubules, preventing their depolymerization, ultimately inducing cell cycle arrest in the mitotic phase, triggering apoptosis. Any alterations in its stereochemistry can drastically diminish binding affinity, thereby reducing its efficacy as a chemotherapy agent. The development of Taxotere (docetaxel) has resulted in improved pharmacokinetics and increased therapeutic effectiveness.[145]

Structural Modifications

Taxotere (docetaxel), a related chemotherapeutic agent with modified stereochemistry, exhibits improved pharmacokinetics and enhanced potency. Hydroxyl and acetyl groups aid in hydrogen bonding, further stabilizing drug-target interactions.[145]

Advances in Drug Optimization

Taxol's stereochemistry remains a critical determinant of its potency, and researchers are continually exploring structural modifications to enhance its therapeutic application. AI-driven molecular docking studies confirm that targeted alterations to these chiral centers can significantly refine Taxol's efficacy.

Determining the stereochemistry of phytochemicals is essential for understanding their biological activity. Various advanced techniques provide structural insights. X-ray Crystallography reveals atomic arrangements through diffraction patterns,[146] while Nuclear Magnetic Resonance (NMR) Spectroscopy analyzes magnetic properties to determine chiral center configurations. Gas Chromatography-Mass Spectrometry (GC-MS) offers high-resolution identification of molecular structures and biological activity.[147] Circular Dichroism (CD) Spectroscopy assesses chiral molecules by measuring differential absorption of polarized light, aiding in absolute configuration determination.[148] Chiral Chromatography separates enantiomers based on their interaction with a chiral stationary phase, establishing their stereochemistry and relative abundance.[149] Combining these methods ensures a comprehensive stereochemical understanding, facilitating the development of precise and effective therapies.

Role of Computational Tools in SAR of Phytochmicals and Future Prospective

The importance of phytochemicals in drug discovery and the rise of computational phytochemistry as a powerful tool for accelerating the process are highlighted. The computational phytochemical pipeline, explaining strategies for compound library diversity, virtual screening, and predictive modeling of biological activity, is discussed. The integration of multi-omics data and computational biology models is also explored. Challenges and future directions in the field are identified, including improving predictive model accuracy, promoting data sharing and collaboration, and addressing ethical and legal considerations. Overall, the significant potential of computational phytochemistry in drug discovery is emphasized, underscoring the need for continued research and development in the field to discover novel and effective therapies for various diseases and conditions.[150]

Quantitative Structure-Activity Relationship (QSAR) Modeling

Computational tools play a significant role in the Structure-Activity Relationship (SAR) analysis of phytochemicals. Quantitative Structure-Activity Relationship (QSAR) modeling is a powerful technique that correlates molecular properties with biological activity. By analyzing vast datasets of phytochemicals and their biological responses, QSAR models can predict the activity of new compounds. Furthermore, QSAR models can identify the specific molecular features responsible for a compound's activity, guiding the design of more potent derivatives. Additionally, QSAR models can screen large virtual libraries of compounds to prioritize promising candidates for further experimental testing.[151,152]

Molecular docking

It is a computational technique that simulates the binding of a phytochemical to a target protein. This information helps understand the mechanism of action and identify potential binding modes. By understanding these binding interactions, researchers can design new compounds with improved affinity and selectivity, leading to the development of more effective drug candidates.[151,153]

Machine learning

A powerful tools for analyzing large datasets of phytochemicals and their biological activities. These algorithms can identify complex patterns within these datasets, enabling the development of predictive models that accurately forecast the activity of novel compounds. Additionally, machine learning techniques can identify the most relevant molecular features that contribute to a compound's activity, providing valuable insights for drug discovery and development.[153,154]

Emerging Role of Artificial intelligence (AI) in Transforming Drug Discovery

Artificial intelligence plays a crucial role in structure-activity relationship (SAR) analysis of phytochemicals by leveraging data-driven molecular analysis to explore correlations between their structures and biological activities. Through predictive modelling, machine learning algorithms forecast the bioactivity, toxicity, and pharmacokinetics of plant-derived compounds, aiding in drug development. AI-powered computational tools such as ChEMBL, SureChEMBL, Enamine, CDD Public and https://www.collaborativedrug.com/ai-drug-discovery for similar structures in secure environment. It also facilitate structural elucidation by determining molecular structures and predicting their interactions with biological targets. Moreover, AI accelerates drug discovery by integrating phytochemical databases with molecular network analysis, optimizing the development process. Additionally, AI-driven metabolomics and genomics approaches decode plant metabolic pathways, uncovering novel bioactive compounds with potential therapeutic applications.[155,156]

AI Applications in SAR of Phytochemicals

AI-driven platforms are revolutionizing drug discovery by analyzing large phytochemical libraries to predict bioactivity and toxicity through high-throughput screening. By enhancing molecular docking and virtual screening, AI aids in identifying promising drug candidates from plant-derived compounds. Deep learning further advances Structure-Activity Relationship (SAR) prediction by modeling intricate connections between phytochemical structures and their biological effects. Additionally, AI-driven metabolomics integrates vast metabolomic data to uncover novel bioactive compounds and their therapeutic potential. To support SAR analysis, AI-powered databases like HerbIntel and CASE provide curated phytochemical data, streamlining the discovery process for natural products with medicinal value.[157]

Prominent AI Tools for SAR in Phytochemicals

HerbIntel is an AI-powered platform designed for molecular network analysis and bioactivity prediction, while CASE serves as a computational tool for phytochemical structural analysis and SAR predictions. Deep learning models contribute to ADMET prediction and molecular property optimization, whereas generative AI and CNNs play a crucial role in de novo drug design and protein structure prediction. CDD Vault functions as an AI-ready scientific data management platform for SAR predictions in medicinal chemistry, while DeepChem provides an open-source deep learning library for molecular property prediction. Additionally, KNIME and Python-based AI models support SAR analysis in phytochemical drug discovery, enhancing the precision and efficiency of research in the field.[155,156]

Big data

Big data analytics tools are essential for integrating diverse data sources, including experimental data, clinical trials, and literature, to gain comprehensive insights into the complex relationships between phytochemicals and their biological activities. By analyzing these large datasets, researchers can uncover hidden patterns and correlations that might not be apparent through traditional methods, accelerating the discovery of novel therapeutic agents. Therefore, by leveraging these computational and AI tools, researchers can significantly accelerate the discovery and development of novel phytochemicals with therapeutic potential. This interdisciplinary approach has the power to transform the field of drug discovery and provide innovative solutions to global health challenges.[153,158]

Green Chemistry in Phytochemicals Drug Discovery

Green Chemistry is a promotion of environmentally friendly drug discovery practices. By leveraging the power of computational tools, researchers can efficiently explore the vast chemical space of phytochemicals, leading to the discovery of novel therapeutic agents. Green chemistry, also known as sustainable chemistry, is a design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. In the context of drug discovery, green chemistry offers a sustainable and environmentally friendly approach to developing new medicines.[159,160]

CONCLUSION

Phytochemicals represent a vast and diverse group of bioactive compounds, crucial for their potential health benefits and therapeutic applications. This systematic review has underscored the importance of phytochemicals, highlighting their extensive classification and significant role in various biological processes. Phytochemicals are classified as alkaloids, flavonoids, terpenoids, and polyphenols. These compounds exhibit broad pharmacological activities, including antioxidant, anti-inflammatory, anticancer, and antimicrobial effects. Understanding the structure-activity relationships (SAR) of phytochemicals is fundamental to unlocking their full potential. SAR studies have provided valuable insights into how specific molecular structures of phytochemicals contribute to their biological activities. This knowledge paves the way for the development of novel therapeutic agents derived from natural sources. Modern computational tools have revolutionized the field of phytochemical research. AI and techniques such as molecular docking, Quantitative Structure-Activity Relationship (QSAR) modelling, and bioinformatics have enabled researchers to predict and analyze the interactions between phytochemicals and their biological targets with more precision. These tools facilitate the identification of promising phytochemical candidates for drug development, thereby accelerating the discovery process and enhancing the efficiency of research efforts. The integration of advanced computational methods with phytochemical studies offers a robust framework for exploring and harnessing the therapeutic potential of these natural compounds. Finally, the information provided helps researchers understand which parts of a molecule are responsible for its effects and how different versions of the same molecule (stereoisomers) might have various activities. This knowledge is crucial for designing effective and safe drugs that will contribute to human health.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

LMW: Low molecular weight; **NO:** Nitric oxide; **IL-1β:** Interleukin-1beta; **TNF-α:** Tumor necrosis factor-alpha; **PGE2:** Prostaglandin E2; **SAR:** Structure activity relationship; **AI:** Artificial intelligence; **UV:** Ultra violet radiation; **AMD:** Age-related macular degeneration; **COX:** Cyclooxygenase; **LOX:** Lipoxygenase; **MAPK:** Mitogen-Activated Protein Kinase; **CDKs:** Cyclin-Dependent Kinases; **DNA-PKcs:** DNA-Dependent Protein Kinase; **PI3K/Akt/mTOR:** Phosphatidylinositol 3-Kinase Protein Kinase B Mammalian Target of Rapamycin; **DNA:** Deoxyribonucleic acid; **NF-κB:** Nuclear Factor kappa-light-chain; **Nrf2:** Nuclear factor erythroid 2-related factor 2; **JNK:** c-Jun N-terminal kinase; **COX:** Cyclooxygenase; **ERK1/2:** Extracellular signal-regulated kinase1/2; **LOX:** Lipoxygenase; **DMC:** Demethoxycurcumin; **BDMC:** Bisdemethoxycurcumin; **THC:** Tetrahydrocurcumin; **BBB:** Blood-brain barrier; **CNS:** Central nervous system; **M6G:** Morphine-6-glucuronide; **CPPPT:** Cyclopentanoperhydrophenanthrene; **LXR:** Liver X receptors; **ABC:** ATP-binding cassette; **ChEMBL:** European Chemical and Molecular Biology Laboratory; **CDD:** Conserved Domain Database; **AI:** Artificial intelligence; **CASE:** Computer-Assisted Structure Elucidation; **ADMET:** Absorption, Distribution, Metabolism, Excretion, and Toxicity; **DeepChem:** Deep learning in life sciences; **KNIME:** Konstanz Information Miner.

AUTHOR CONTRIBUTIONS

Mohd and SSA: Conceptualized, designed, drafted, supervision, and critical revision the manuscript. AVR: Interpretation, Editing, admin and technical support of the manuscript. All authors have read, reviewed, and approved the final manuscript.

ETHICAL STATEMENTS

The authors declare that this systematic review, titled "Current Status on Phytochemicals Classification, Steucture-Activity Relationship, Stereochemistry, and AI-Driven Applications: A systematic Review" is conducted with strict adherence to ethical research practices. The study ensures transparency, integrity, and accuracy in data collection, interpretation, and reporting. All sources and references are appropriately cited to acknowledge the contributions of previous research.

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