SECONDARY METABOLITES IN PLANTS: STRUCTURE, BIOSYNTHESIS, BIOACTIVE PROPERTIES

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Abstract. *Medicinal plants' diverse and multifaceted pharmacological effects are primarily based on their phytochemical components. These components are generally divided into two groups based on their involvement in basic metabolic processes: primary and secondary metabolites. Primary plant metabolites are involved in essential life functions and are fairly consistent in all living cells. Conversely, secondary plant metabolites are the products of auxiliary pathways, such as the shikimic acid pathway. In the study of the medicinal properties of herbs, secondary plant metabolites are the focus of attention. These compounds have played an important role in traditional and folk medicine in alleviating various ailments. A good understanding of the chemical composition of plants leads to a better appreciation of their potential medicinal value. Secondary metabolites of plants are numerous chemical compounds produced by plant cells through metabolic pathways derived from primary metabolic pathways. Each plant family, genus and species produces a specific mixture of these secondary metabolites, sometimes contributing to the taxonomic classification of plants. In modern medicine, they have served as starting points for developing drugs to treat a wide range of conditions. Secondary plant metabolites are classified into different classes based on their chemical structures. In this review, we will explore the different categories of plant secondary metabolites, their localisation in the plant, their biosynthesis and their significant bioactivities.*

Keywords: *secondary metabolites, phenolics, terpenes, alkaloids, biosynthetic pathway*

INTRODUCTION

Secondary metabolites in plants are highly diverse and fascinating phytochemicals that accumulate in plant tissues and fulfil several important roles. These substances are thought to have important functions, such as protecting plants from insect invasion, herbivores and disease. The production of secondary metabolites can vary depending on the environment or the nutrient resources available to the organism.

These compounds may be detectable within a species only during certain stages of growth and development or may be triggered only during periods of stress caused by microbial aggression or nutrient depletion. Secondary metabolites have diverse biological effects and provide a scientific basis for using medicinal plants in traditional medicine in many ancient societies.

These secondary metabolites manifest various pharmacological properties, which can be classified based on their chemical structure and the functional groups they contain. They are remarkable reservoirs of individual bioactive constituents in nutraceuticals and modern pharmaceuticals. In addition, secondary metabolites possess impressive antioxidant properties, making them valuable natural sources of antioxidants in nutraceuticals.

A large number of secondary metabolites also exhibit a broad spectrum of therapeutic effects, directly interacting with receptors, cell membranes and nucleic acids.

Secondary metabolites are usually classified according to their biosynthetic pathways into three main groups: phenolics, terpenes and alkaloids.

Phenolics

Chemical structure and localisation of phenolics in plants

Phytochemical substances known as phenolic compounds are highly prevalent in the plant kingdom and hold substantial significance in plants' physiological and morphological aspects. Phenolic compounds are found throughout the plant kingdom, identified in high concentrations in the epidermis of leaves and fruits, playing important and extremely diverse roles. These compounds are essential for promoting plant growth and reproduction, offering defence mechanisms against pathogens and predators (BRAVO, L., 1998). Additionally, they play a key role in determining the colour and sensory attributes of various fruits and vegetables (ALASALVAR, C., 2001).

From a structural perspective, phenolic compounds consist of an aromatic ring accompanied by one or more hydroxyl substituents. These compounds vary from simple phenolic molecules to highly polymerised compounds (BRAVO, L., 1998). Despite their structural diversity, this category of compounds is commonly referred to as polyphenols.

The majority of naturally occurring phenolic compounds are found in a conjugated form with mono- and polysaccharides linked to one or more phenolic groups. Functional derivatives, such as esters and methyl esters, are also present. Among the main biologically active compounds are phenolic acids, flavonoids, tannins, isoflavonoids, anthocyanins, quinones, and stilbenes.

Phenolic acids can be categorised into two subgroups: hydroxybenzoic acids and hydroxycinnamic acids. Hydroxybenzoic acids comprise gallic acid, p-hydroxybenzoic acid, protocatechuic acid, vanillic acid, and syringic acid. These acids all have a common C6-C1 structure. Examples of hydroxycinnamic acids include caffeic acid, ferulic acid, and p-coumaric acid. Hydroxycinnamic acids, conversely, are aromatic compounds with a side chain composed of three carbon atoms (C6-C3).

Flavonoids comprise plants' most prominent group of phenolic compounds, featuring a low molecular weight and comprising fifteen carbon atoms arranged in a C6-C3-C6 structural configuration. These natural phenolic compounds can be found in plants as aglycones or in their free form. They are widely present in the plant kingdom in flowers, leaves, fruits and vegetables. The primary categories of flavonoids include flavonols, flavones, flavanones, flavanols, isoflavones, flavanones, and anthocyanidins.

Tannins are high-molecular-weight compounds that belong to the third major group of phenolic substances. They can appear in leaves, tree bark, and fruits. Tannins are classified into two types: hydrolysable tannins and condensed tannins. The former comprises esters of gallic acid (gallotannins and ellagitannins), while the latter, also identified as proanthocyanidins, consists of polymers of polyhydroxyflavan-3-ol monomers (PORTER, L.J., 1989).

Isoflavonoids are chemical compounds that fall under the flavonoid family and are distinguished by their B ring fused to the C3 position of the C ring. These phenolic compounds are naturally occurring and display phytoestrogenic activity, indicating their ability to act as estrogens in plant organisms, and are primarily found in leguminous plants.

Anthocyanins represent the largest and most significant group of water-soluble pigments located in vacuoles, accountable for colours like red, blue, and purple in the majority of fruits, flowers, vegetables, and cereals (SHAHIDI., F., 2004). They are present in leaf, stem, seed, and root tissue. Anthocyanins are highly reactive compounds found in plant tissues. The fundamental structure of anthocyanins is anthocyanidin. Anthocyanins are

formed by the binding of anthocyanidins to carbohydrates in plant tissues. There have been 23 different types of anthocyanidins identified, with the most commonly occurring ones being pelargonidin, cyanidin, peonidin, delphinidin, petunidin, and malvidin. Cyanidins are the most widespread group of naturally occurring anthocyanins and are followed by delphinidin.

Quinones are a phenolic compound with a fully conjugated cyclic dione structure, like benzoquinones. They are derived from aromatic compounds by converting an even number of –CH= groups into –C(=O)– groups, with any necessary rearrangement of double bonds. Plants' most common basic structures of quinones are p-quinone, o-quinone, anthraquinone, naphthoquinone, and naphthodianthrone.

Stilbenes comprise a class of phenolic compounds with a chemical structure resembling flavonoids, wherein methylene bridge links the two aromatic rings. Trans-resveratrol is among the most prominently recognised stilbenes, which mostly manifests as a glycosylated phytoalexin elicited in certain plants following exposure to fungal pathogens.

Biosynthetic pathway for phenolics

Phenolic compounds are primarily produced through the malonic and shikimic acid pathways. These pathways are present in both eukaryotes and prokaryotes, with some exceptions. Higher plants lack the malonic acid pathway, while animals do not possess the shikimic acid pathway. The synthesis of various aromatic amino acids within the shikimic acid pathway utilises precursor molecules from glycolysis and the pentose phosphate pathway, with phenylalanine being a commonly produced product (AHMED., E., 2017).

Bioactive properties for phenolics

The impact of phenolic compounds found in plants on human health and disease prevention and treatment are varied, including their role as antioxidants, antibacterial agents, anti-cancer agents, anti-inflammatory agents, and protectors against U.V. radiation damage to the skin.

Antioxidants activity

Due to their antioxidant properties, flavonoids and phenolic compounds are widely recognised as the largest phytochemical molecules (CHOUDHARY, P., 2021). Traditional Chinese medicinal plants that contain phenolic acids and flavonoids have been found to display high antioxidant activity. *Nepeta italica subsp. Cadme*a and *Teucrium sandrasicum* are rich sources of phenols, tannins and flavonoids, demonstrating antioxidant and cytotoxic properties. *Bauhinia variegata L.* contains flavonoid compounds and has antioxidant properties by neutralising radicals, binding iron and reducing capacities (MISHRA., A., 2013). Extracts from the rhizome of *Polygonatum verticillatum (L.) All* demonstrate antioxidant activity, which correlates with the level of phenolic composition (KUMAR SINGH, 2018). SINGH AND YADAV (2022) report that oregano, cloves, thyme, and rosemary have the highest phenolic compounds among medicinal plants. Oligomers and monomers of flavan-3-ols with high antioxidant capacity were discovered in *Camellia fangchengensis* (MENG, 2018).

Antibacterial activity

Asplenium nidus L. contains gliricidin 7-O-hexoside and quercetin-7-O-rutinoside, which exhibit antibacterial activity against three pathogenic agents, namely *Proteus vulgaris Hauser*, *Proteus mirabilis Hauser*, and *Pseudomonas aeruginosa (Schroeter) Migula* (JARIAL., R., 2018). Flavones, derived from the root of *Scutellaria baicalensis Georgi*, have shown potential antibacterial properties against skin inflammation caused by *Propionibacterium acnes* in both in vitro and in vivo models (TSAI., P., J., 2016). Kaempferol, extracted from *Impatiens balsamina L.*, has demonstrated the potential to inhibit the growth of *P. acnes* (LIM, Y.-H., 2007). Furthermore, the extract of *Mangifera indica L.* contains

phenolic compounds that exhibit anti-acne properties by also inhibiting the growth of *P. acnes* (POOMANEE, W., 2018).

Antitumoral activity

Phenolic compounds, specifically flavonoids, are widely acknowledged as chemopreventive agents in cancer therapy, as stated in previous studies (AHMED., S.I, 2016, BLOCK V., 1992, BRUSSELMANS, K., 2003). In the case of combating malignant melanoma, *Curcuma longa L.* rhizome extract has demonstrated potential as a natural source of active compounds with anti-cancer properties, as evidenced by its performance in the murine melanoma cell line B164A5 (DANCIU, C., 2015). Gliricidia 7-O-hexoside and Quercetin 7-O-rutinoside, flavonoids extracted from the medicinal fern *Asplenium nidus*, have been identified as promising chemopreventive agents against human hepatoma HepG2 and human carcinoma HeLa cells (RICHANE, A.,2022). Quercetin has shown the ability to induce miR-200b-3p and regulate the self-renewal mode of pancreatic cancer divisions (NWAEBURU, C.C, 2017). Genistein, a soy isoflavone, has been observed to inhibit the activation of the nuclear factor kappa B (NF-KB) signalling pathway. This pathway is responsible for maintaining the balance between cell survival and apoptosis. Additionally, genistein has been shown to act against cell growth, apoptosis, and metastasis, including epigenetic changes in prostate cancer (ADJAKLY, M., 2013). Curcumin, a phenolic compound, has exhibited antitumor effects on skin cancers by influencing the cell cycle and acting as a pro-apoptotic agent (DAZIALO., M., 2016). Curcumin acts as a non-selective inhibitor of cyclic nucleotide phosphodiesterase (P.D.E.) to prevent the proliferation of melanoma cells, which is linked to the epigenetic integrator UHRF1 (ABUSNINA, A., 2011). Additionally, curcumin inhibited the proliferation of certain cell lines in prostate cancer and induced apoptosis in a response dependent on dose (IDE, H., 2018).

Anti-inflammatory activity

Hydroxytyrosol and quercetin 7-O-α-L-rhamnopyranoside possess anti-inflammatory properties by reducing tumour necrosis factor-alpha (TNF-α) levels. Similarly, at a concentration of 100 μm, hydroxytyrosol and caffeic acid demonstrated substantial anti-inflammatory activity by lowering the release of nitric oxide (NO) in macrophages stimulated by L.P.S., an endotoxin from gram-negative bacteria. The activity was comparable to the positive control indomethacin (KIRMIZIBEKMEZ, H., 2019). The main chemical compounds extracted from *Cardiospermum halicacabum* through ethanol extraction were chrysoeriol, kaempferol, apigenin, luteolin, methyl 3,4-dihydroxybenzoate, 4-hydroxybenzoic acid, quercetin, hydroquinone, protocatechuic acid, gallic acid, and indole-3-carboxylic acid. A study showed that these compounds possess high anti-inflammatory and antioxidant properties (CHENG, H.-L., 2013). The anti-inflammatory potential of polyphenolic compounds extracted from *Gaillardia grandiflora Hort. ex Van Houte* and *Gaillardia pulchella Foug*, both of Egyptian origin, was examined by MOHARRAM F.A (2017). Additionally, COMPAORE, M. (2018) identified and reported on the anti-inflammatory activity of extracts from *Bidens engleri O.E. Schulz*, a member of the *Asteraceae* family, and *Boerhavia erecta L.*, belonging to the *Nyctaginaceae* family. *Plantago subulata* exhibited anti-inflammatory properties on macrophages and a protective effect against H2O2-induced damage (GENC., Y., 2019).

Protection of the skin against U.V. radiation

Quercetin is a flavonol in apple peel, onion skin, and *Hypericum perforatum L.* leaves (WACH., A., 2007). The topical application of quercetin effectively suppressed skin damage caused by ultraviolet radiation in hairless mice (CASAGRANDE, R., 2006). Silymarin is a standardised extract of flavonolignins obtained from milk thistle fruits (*Silybum marianum (L.) Gaernt.*), which contains silibinin, a primary active constituent (BIJAK., M.,

2017). Topical application of silymarin promoted the repair of D.N.A. damage induced by UVB radiation, which consequently prevented apoptosis in UVB-exposed human epidermal keratinocytes and fibroblasts, according to an in vitro study (KATIYAR., S.K., 2011). Genistein, a soy isoflavone, has been reported to possess photoprotective properties in an in vitro model equivalent to human skin by inhibiting UV-induced D.N.A. lesions (MOORE., J.O., 2006).

Terpenes

Chemical structure and localisation of terpenes in plants

Terpenes are the most extensive and varied group of naturally occurring compounds found in plants. They are responsible for plants' fragrances, tastes and pigments (JOSHEE, N., 2019). The term "terpene" was coined by Dumas in 1866 and originated from the Latin word "terebintina" (*Balsamum terebinthinae*), a liquid extract obtained from pine trees (NINKUU, V., 2021). Isoprene, which has the molecular formula C5H8, serves as the fundamental unit for terpenes in chemical terms. Therefore, the molecular formulas of terpenes can be expressed as (C5H8) n, where n is the number of linked isoprene units. The diverse structures of terpenes arise from isoprene units' capacity to create linear chains through head-to-tail binding or to form rings.

Terpenes can be classified into seven categories based on their carbon chain length, namely hemiterpenes (C5), monoterpene (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25), triterpenes (C30), and tetraterpenes (C40) (DEWICK, P. M., 2009).

Hemiterpenes (C5) consist of a single isoprene unit and only a few of these compounds occur
naturally. Isoprene is a volatile compound abundantly released by many plant species, notably deciduous trees such as oak, willow, poplar, and fir (DEWICK., P. M., 2009).

Monoterpenes (C10) comprise two isoprene units obtained from various flowers, fruits, and leaves. Monoterpenes are recognised as crucial elements in essential oils and perfumes. They are the most aromatic members of the terpene family. One of their key functions involves drawing in pollinators while deterring plant-consuming organisms (JOSHEE, N., 2019). The classes of monoterpene comprise acyclic, monocyclic and bicyclic variations.

Diterpenes (C20) are composed of four isoprene units and have the formula C20H32. They demonstrate inhibitory effects against pathogenic microorganisms, herbivorous pests, and weeds from different sources. These highly promising biological activities position them as essential agricultural secondary metabolites with the potential for biopesticide production (DE SOUSA, 2018). Naturally occurring diterpenes comprise abietatriene, located in the *Cryptomeria japonica* plant (family *Cupressaceae*), and abietane, found in the resins and tissues of gymnosperms.

Sesterterpenes (C25) are formed of 5 isoprene units, and their formula is C25H40. These are in fungi and marine organisms (DEWICK., P. M., 2009).

Triterpenes (C30) consist of 6 isoprene units. The predominant triterpene structures comprise pentacyclic structures such as oleanane, ursane, taraxerane, taraxastane, and lupane, as well as tetracyclic ones like dammarane and cucurbitane. Triterpenes, particularly the pentacyclic variants, are secondary metabolites that broadly distribute across the plant kingdom, manifest in leaves, stem bark, fruits, and roots (NAZARUK, J., 2015).

Tetraterpenes (C40) comprise 8 isoprene units. Carotenoids represent a single group of compounds within tetraterpenes. These compounds facilitate photosynthesis and are found in non-photosynthetic plant tissues, fungi, and bacteria (DEWICK., P. M., 2009). Natural carotenoids consist of lycopene and β-carotene. Lycopene is the characteristic carotenoid

pigment of mature tomatoes (*Lycopersicon esculentum*, *Solanaceae* family), while the orange hue of carrots (*Daucus carota*, *Umbelliferae*/Apiaceae family) arises due to β-carotene.

Biosynthetic pathways for terpenes

Terpenes can be synthesised through two distinct pathways: the cytosolic pathway, also recognised as the mevalonic acid pathway, and the chloroplast pathway, or methylerythritol-4-phosphate pathway (M.F.P. pathway). The cytosolic pathway is unique to eukaryotes and is responsible for producing substances such as triterpenes, sesquiterpenes, sterols, and brassinosteroids, while the chloroplast pathway is present in prokaryotes and the plastids of eukaryotic cells. It produces hemiterpenes, mono-, di-, and tetra-terpenes, isoprene, carotenoids, and phytohormones. The process of the mevalonic acid pathway commences with the condensation of three molecules of acetyl-CoA, resulting in the creation of mevalonic acid. Mevalonic acid then undergoes phosphorylation to produce mevalonate-5-phosphate as the product of the reaction. This substance is subsequently employed in fabricating isopentyl diphosphate (IDP), a forerunner for the biosynthesis of all terpenes. In contrast, within the methylerythritol-4-phosphate (M.E.P.) pathway, pyruvate and glyceraldehyde-3-phosphate amalgamate to produce methyl erythritol-4-phosphate, which is further utilised to create 4-hydroxy-3-methylbut-2-enyl diphosphate (H.M.B.D.P.). H.M.B.D.P. is an important intermediary that eventually results in the creation of either isopentyl diphosphate (IDP) or dimethyl-allyl-diphosphate (D.M.A.P.P. or D.M.A.D.P.) (AHMED., E., 2017).

Bioactive properties for terpenes

Several studies indicate that terpenes play a critical role in promoting human well-being. These bioactive substances, consisting of several isoprene units, make up the majority of organic compounds formed in the essential oils of diverse plants. They significantly impact the treatment of various diseases, and numerous in vitro and in vivo studies demonstrate their effectiveness in providing anti-cancer, antimicrobial, anti-inflammatory, antioxidant, and antiallergic. (ZHAO, D.-D., 2016)

Antitumoral activity

SHEIKH ET AL. (2017) researched the impact of citral on human colorectal cancer cells HCT116 and HT29 proliferation. The findings revealed that citral noticeably decreased the expression of Bc-2 and Bcl-xL. Another compound reported to have anti-cancer properties is α-Thujone, which Pudelek et al. (2019) investigated for its effect on the malignancy of glioblastoma multiforme (G.B.M.) cells. α-Thujone has been found to have a mitigating effect on the proliferation and viability of G.B.M. cells, as well as anti-invasive and pro-apoptotic effects. According to POTOČNJAK and colleagues (2018), carvacrol has demonstrated antitumoral activity against HeLa cells, a human cervical cancer cell line, inducing cytotoxicity. Carvacrol shows promise as a potential source of antitumor activity against human gastric adenocarcinoma cells (A.G.S.). Its effects include inhibiting A.G.S. cell proliferation, demonstrating genotoxicity, and reducing glutathione levels (GÜNES-BAYIR, A., 2017).

Antibacterial activity

Terpenoid compounds exhibit bactericidal effects (GUIMARAES, A.C., 2019). For instance, limonenes have synergistic modulating effects with the antibiotic gentamicin in inhibiting Gram-positive bacteria such as *Staphylococcus aureus* and Gram-negative bacteria like *Escherichia coli* as well as multiple resistant bacteria (COSTA, M.D.S., 2019). Furthermore, a combination of limonene and ε-polylisine has been found to have an additive, synergistic effect against *E. coli*, *S. aureus*, *Bacillus subtilis*, and *Saccharomyces cerevisiae* (ZAHI, M.R., 2017). The isomers of the monoterpene terpineol (α-terpineol, terpinen-4-ol, and

δ-terpineol) exhibit effective inhibitory activity against various Gram-negative bacteria, particularly *Shigella flexneri*, due to bacterial membrane permeability mechanisms. The aforementioned mechanisms result in the discharge of nucleic acids and proteins, accompanied by a decline in the membrane potential (HUANG., J., 2021).

Anti-inflammatory activity

In recent decades, studies have demonstrated the significant role of terpenes in reducing inflammation-related symptoms. This is attributed to their inhibiting various pathological steps in the inflammatory process (KIM, T., 2020). Inflammation is a defensive response of the host to foreign agents, usually caused by microbial infections or tissue damage. Dysregulation of inflammatory responses may induce acute and chronic inflammatory disorders, resulting in excessive or prolonged tissue injury (CHEN, L., 2017). Terpenes' efficacy in mitigating inflammation has been demonstrated, including reducing respiratory inflammation, atopic dermatitis, arthritis, and neuroinflammation (KIM, T., 2020). Myrcene's potential anti-inflammatory impact on renal inflammation was tested in adrenalectomised rats. The mechanism identified appears to be linked with the reduction of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) and anti-inflammatory markers (IL-4 and IL-10), coupled with the rise in endogenous antioxidants, including catalase (C.A.T.), superoxide dismutases (S.O.D.) and glutathione (G.S.H.) (ISLAM, A. U. S., 2020). Limonene, a cyclic monoterpene, has been found to possess gastroprotective properties in rats. Its exact mechanism for gastroprotection is yet to be determined. However, existing experimental data indicates that its effects may stem from its ability to regulate oxidative stress and mitigate inflammatory responses via inhibiting gene expression mediated by NF-κB (DE SOUZA, 2019). Several terpenes, including (-)-β-pinene and (+)-α-pinene, have been found to decrease the expression of inflammation-associated genes (IL-4 and IL-13) and the secretion of β-hexosaminidase in LPS-stimulated RBL-2H3 cells. The article by Yang, Choi, Kim, Eom and Park from 2021 discusses the potential use of these compounds in treating inflammatory conditions and their role in developing novel anti-inflammatory drugs. α-Pinene, present in essential oils from conifers, has been researched for its capability to protect against the inflammatory response in human epidermal keratinocytes (KARTHIKEYAN, R., 2018). The researchers concluded that α-pinene inhibits the expression of inflammatory proteins that UVA induces, such as TNF-α and IL-6.

Antioxidant activity

Certain essential oils notably impact decreasing oxidative stress and may be employed to prohibit particular chronic illnesses. Chamazulene, a bicyclic sesquiterpene derivative present in *Matricaria chamomilla* essential oils, has been successful in controlling the levels of reactive oxygen species (R.O.S.) in bovine aortic endothelial cells-1 (B.A.E.C.s) (QUERIO, G., 2018).

Antiallergic activity

Allergic conditions involve an inflammation with the infiltration of T cells and granulocytes such as eosinophils, neutrophils, and mast cells, the latter of which has a crucial role in the final phase of most allergic reactions (MODENA, B.D., 2016). Studies have investigated certain terpenes for their antiallergic properties. Atractylone (Atr), a sesquiterpene constituent of *Atractylodes japonica*, suppresses the degranulation of peritoneal mast cells in rats (R.P.M.C.s), leading to the release of tryptase and histamine. In light of these findings, Atractylone possesses therapeutic potential for managing mast cell-mediated allergic reactions (HAN, N.-R., 2016).

Alkaloids

Chemical structure and localisation of alkaloids in plants

Alkaloids are small organic compounds containing nitrogen, mainly present in plants but also found in microorganisms and animals to a lesser degree. It has been reported that more than 27,000 alkaloid structures have been identified, of which 21,000 are derived from plants. Plant alkaloids are primarily known in the scientific literature for their role in protecting against herbivores due to their bitter taste, ability to disrupt protein function after ingestion and metabolism, and impact on the central nervous system (HARBORNE, J., 1993). To reduce the risk of self-intoxication, defence compounds are often stored in vacuoles or an apoplastic compartment with limited metabolic activity (MITHÖFER, A., 2012).

Most alkaloids comprise carbon, oxygen, hydrogen, and nitrogen, but occasionally phosphorus, chlorine, sulphur, and bromine are present in the structures. The quantity of nitrogen atoms in a molecule fluctuates from one (cocaine) to five (ergotamine). It is noted that nitrogen atoms are commonly found in alkaloid molecules as a constituent of a heterocyclic ring (for example, quinine, reserpine and strychnine). However, certain alkaloids exhibit nitrogen atoms within their aliphatic side chains (such as ephedrine and mescaline). Tertiary amines make up the majority of nitrogen atoms in alkaloids (examples include morphine and reserpine), with secondary amines (ephedrine) and primary amines (pseudoephedrine) exhibiting much less frequency (NICOLAOU, K.C., 2011).

Alkaloids can be classified based on the heterocyclic structure of their base into two groups. The first group, non-heterocyclic alkaloids, includes hordenine, mescaline, colchicine and taxol. The second group, heterocyclic alkaloids, is further subdivided into four categories based on the chemical ring structure: piperidinic (conine, piperine, lobeline, lobelanine), pyridinic (nicotine, anabasine, niacin), pyrrolidinic (hygrine, cuscohygrine, stachydrine) and quinolinic (quinine, quinidine). Isoquinoline alkaloids (including morphine, papaverine, chelidonine, and berberine), tropane alkaloids (such as atropine, cocaine, and hyoscyamine), pyrrolizidine alkaloids (including retronecine and senecionine), and indole alkaloids (such as yohimbine, reserpine, and vinblastine) are under investigation for their medicinal properties (KAR, A, 2007).

Alkaloids are present in specific plant parts, including leaves, seeds, roots, bark, and fruit capsules, within secretory channels. Only certain plant tissues can synthesise alkaloids, while they can also gather in other tissues. Nicotine, an alkaloid from the tobacco plant *Nicotiana tabacum (Solanaceae*), is generated in the roots and then transported to the leaves, where it accumulates.

Biosynthetic pathways for alkaloids

The synthesis of alkaloids primarily depends on using pyruvate and shikimic acid. These organic molecules are derived from phosphoenolpyruvate and erythrose-4-phosphate. In the process, L-amino acids such as aspartic acid, lysine, tryptophan, and tyrosine perform a fundamental function in forming most major alkaloids. It is noteworthy that purine alkaloids are an exception as they originate from xanthosine, and pyrrolizidine alkaloids are derived from putrescine and spermidine (AHMED., E., 2017).

Bioactive properties for alkaloids

Alkaloids have multiple medicinal uses. They possess antitumor properties, and their potential for antidiabetic, antibacterial and antifungal activities is currently under investigation.

Antitumoral properties of alkaloids

One of the main challenges in cancer treatment is the emergence of multidrug resistance to chemotherapy agents, primarily caused by drug efflux mediated by P-

glycoprotein (JOSHI, 2017). Therefore, plant alkaloids have generated interest in medicinal chemistry and medicine due to their ability to act as anti-cancer agents in drug-resistant cancer subtypes. Alkaloids research has suggested alkaloids as a possible preventive or management measure for cancer-related oxidative stress and inflammation, according to ALASVAND'S (2019). Specifically, vinblastine, vincristine, vindesine, and vinorelbine - alkaloids present in the *Vinca* family - have shown anti-tumour properties against different types of cancer cells, including breast cancer cells like MCF-7 and MDA-MB-231, as well as liver cancer cells (HepG2, HepG2/A.D.M.), and a leukaemia cell line (K562) (ZHENG, J., 2013). Drug resistance is a prevalent concern during chemotherapy, and certain cell lines resistant to specific chemotherapeutic agents are responsive to alkaloid therapy. In a study by Wang and colleagues (2017), MCF-7TXT, a cell line resistant to docetaxel, was subjected to colchicine treatment. The study's authors discovered that the MCF-7TXT cells exhibited superior cytotoxicity against vinorelbine and vinblastine alkaloids compared to the non-resistant MCF-7cc cell line.

Furthermore, the study by Wang (2017) showed that MCF-7 cells, resistant to docetaxel, were resistant to *Vinca* alkaloids. However, these cells were sensitive to colchicine, 2MeOE2, ABT-751 and CA-4P, deemed some of the most reliable antineoplastic drugs used to treat breast cancer. As previously mentioned, drug resistance is a persistent problem in cancer patients undergoing chemotherapy. For example, thymidylate synthase enzyme levels are elevated in non-small cell lung cancer tissue during pemetrexed therapy. Chiu and colleagues (2017) found that *Vinca* alkaloids successfully suppressed the growth of pemetrexed-resistant tumours in both in vivo studies with vinblastine and in vitro studies with vincristine. *Vinca* alkaloids regulate the ERK-mediated pathway, important in controlling pemetrexed-induced apoptosis. In addition, compounds that bind to tubulin, interfering with microtubule assembly and causing mitotic arrest, are among the most commonly used and significant antitumor agents (CHIU, L.Y., 2017).

Nevertheless, most of these compounds have cytotoxic properties, thus suggesting the need for ongoing research into new natural compounds. For instance, vinblastine, vincristine, vindesine, and vinorelbine are established antimitotic medications, and ZHENG ET AL. (2013) demonstrated that variances in these compounds' structures can alter their antitumor effects and toxicity. The alkaloids were found to display a moderate antitumor activity in the MCF-7, MDA-MB-231, HepG2, HepG2/A.D.M. and K562 cell lines, suggesting that the effect is mediated by electron-attracting substituents in the ring structure. Their findings demonstrate that papaverine could hinder the growth of these cells in human glioblastoma. In 2019, Inada and fellow researchers assessed the potential use of papaverine alkaloid as an antitumor agent in human glioblastoma (G.B.M.) by testing its effectiveness on temozolomide-sensitive U87MG cells and temozolomide-resistant T98G cells.

Antidiabetic properties of alkaloids

Several reports have presented encouraging studies on the potential antidiabetic effects of alkaloids in numerous plants, including *Rhizoma coptidis*, *Trigonella foenum-graecum*, *Berberis vulgaris*, and *Ervatamia microphylla*. These alkaloids exhibit antidiabetic properties through various mechanisms, including reducing insulin resistance, promoting insulin secretion, and improving intestinal microbiota structures, among others (ZHOU J., 2012). Alkaloids extracted from *Coptis chinensis*, including berberine, epiberberine, coptisine, palmatine, and magnoflorine, have been associated with anti-obesity properties. In a study by CHOI ET AL. (2014), alkaloids from *Coptis chinensis* decreased adipogenesis in 3T3-L1 cells, and their effectiveness was dose-dependent without any apparent cytotoxic effects. Additionally, plant alkaloids have the potential to act as antidiabetic agents, as they

strongly inhibit the activity of α-glucosidase. CHOI ET AL. (2015) reported that alkaloids from the rhizome of the *Coptis chinensis* plant, specifically berberine, epiberberine, magnoflorine, and coptisine, have antidiabetic properties by potentially inhibiting protein-tyrosine phosphatase 1B (PTP1B). PTP1B, an enzyme linked to non-insulin-dependent diabetes mellitus onset through its overproduction, is a non-transmembrane protein-tyrosine phosphatase. The authors found that the tested alkaloids had inhibitory effects on PTP1B, with IC50 values of 16.3, 24.19, 28.14, and 51.04 μM, respectively. They noted that berberine and epiberberine had mixed inhibition, while magnoflorine and coptisine were non-competitive. A study conducted by Hulcová and colleagues (2018) indicates that alkaloids found in the *Amaryllidaceae* family possess inhibitory potential against glycogen synthase kinase 3β. The authors reported 28 alkaloids of seven structural categories, including belladine, hemanthamine, crinine, galantamine, lycorine, tazettine, and homolycorine. Inhibitory activity against glycogen synthase kinase 3β greater than 50% was only observed in caranine, 9-O-demetilhomolycorine, and masonine. ULLAH ET AL. (2018) found that rats with induced diabetes treated with steroidal alkaloids from *Sarcococca saligna* at a subcutaneous dosage of 5mg/kg experienced reduced blood glucose levels. The reported effect was attributed to sarcovagine-D and holaphylline, which were also correlated with a significant improvement in blood lipids. It is crucial to note that aberrant lipid levels in individuals with diabetes mellitus may develop hypertriglyceridemia and hypercholesterolemia in the bloodstream. Four-week research by ZHANG ET AL. (2018) exhibited that the alkaloids found in the bark of *Litsea glutinosa*, when given to mice at doses of 50, 100, and 200 mg/kg, decreased the body weight and fat content, without affecting the average food intake of the treated mice. The effectiveness of this treatment was similar to that of metformin.

Moreover, at concentrations of 100 to 200 mg/kg, alkaloid extracts from L. glutinosa resulted in a notable decrease in fasting blood glucose levels, glycosylated haemoglobin, and glycosylated serum proteins. In addition, the study illustrated that the alkaloid extract from *L. glutinosa* notably boosted hepatic glucokinase activity, a pivotal enzyme in glycogen synthesis, and increased hepatic glycogen content. Chronic inflammation is frequently observed in individuals with diabetes and can result in insulin resistance. Alkaloid treatment has significantly decreased inflammation markers, including MCP-1, TNF-α and IL-6. Alkaloids possess the potential to function as antidiabetic agents by modulating blood glucose and lipid levels. An illustration of this was evident when alkaloids sourced from Capparis decidua resulted in a 44% decrease in glucose-6-phosphatase. This was observed in diabetic mice induced by streptozotocin. Additionally, the alkaloid treatment improved glycogen content in the liver and muscles by 33% and 28%, respectively. (SHARMA, B., 2010)

Antibacterial and antifungal properties of alkaloids

Alkaloids obtained from *Chelidonium majus Linn*. exhibit antifungal activity against drug-resistant yeast strains, as reported by MENG F. in 2009. Imidazole derivatives, with significant therapeutic potential and antibacterial activity, were discovered by DE LUCA in 2006. Cycloanine and cocsoline alkaloids isolated from *Albertisia villosa* were found to possess antibacterial and antifungal properties by LOHOMBO-EKOMBA and colleagues in 2004. HYMETE ET AL. (2005) reported that the inhibitory activity of *Echinops ellebeckii* and *Echinops lingisetus* against *Candida albicans* and *Staphylococcus aureus* is attributed to their alkaloids, saponins, and phenols. Quinoline alkaloids, namely skimmianine, kokisaginina, and masculina, which were extracted from the *Raulinoa echinata*, have exhibited antifungal

action against the *Leucoagaricus gongylophorus* fungus and against the *Trypanosoma cruzi* tripomastigote forms in vitro (BIAVATTI, M.W., 2002).

CONCLUSIONS

Given the many ways they impact our lives, it is not easy to imagine humanity without plants. These botanical entities are not only essential for nourishing our bodies, but they also form the basis of modern medicine. Plants have long been utilised for medicinal purposes, but in today's world, their potential for improving human health is gaining recognition due to their widespread availability, affordability and reduced risk of adverse effects.

Plants have long been utilised for medicinal purposes, but in today's world, their potential for improving human health is gaining recognition due to their widespread availability, affordability and reduced risk of adverse effects. Despite their vast benefits, the potential of plants remains largely untapped. Historically, medicinal plants and their derivatives have played an increasingly prominent role. This development has demanded extensive exploration and research within medicinal plants, aiming to expose potential avenues for furthering these natural resources. The goal is to cultivate novel and useful medicinal compounds from them.

The aforementioned secondary metabolites play a crucial role in the healthcare system due to their exceptional pharmacological and biological properties. Such compounds merit a crucial position within the healthcare field. They serve as natural precursors for most synthetic drugs and effectively bridge the gap between the natural and synthetic worlds of medicine. Hence, there is significant potential for the efficient utilisation and investigation of these compounds in modern medical research to discover new pharmaceutical agents**.**

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