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Natural P-glycoprotein Inhibitors in Circumventing Multidrug Resistance

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KEYWORDS

Medicinal plants; multidrug resistance; natural inhibitors; p-glycoprotein; pharmaceutical sciences.

ABSTRACT:

Introduction: Multidrug resistance (MDR) remains a formidable challenge in pharmaceutical intervention and continues to hinder the successful clinical management of many diseases, particularly cancer. P-glycoprotein (P-gp), a 170-kilodalton ATP-driven integral membrane protein, is a key regulator of MDR, functioning as a protective barrier against xenobiotics. Its overexpression in cancer cells markedly reduces intracellular concentrations of chemotherapeutic drugs, thereby limiting their effectiveness. Understanding the molecular mechanisms underlying drug resistance is vital for formulating approaches that can overcome this obstacle and enhance treatment outcomes. Natural inhibitors, known for their minimal toxicity and easy accessibility, hold significant potential for semi-synthetic modification. Such derivatives may provide new scaffolds valuable for developing effective MDR reversal agents.

Objectives: This review aims to provide a scientifically curated overview of natural P-gp inhibitors, emphasizing their mechanistic pathways and binding interactions involved in MDR reversal.

Methods: Findings from extensive *in vitro, in vivo* and *in silico* studies highlight the therapeutic potential of 100 natural P-gp inhibitors derived from 200 medicinal plants.

Results: Several bioactive compounds demonstrated promising MDR-modulatory properties. Detailed insights into their interactions with key residues of P-gp, may facilitate rational drug design and inform synergistic combination therapies.

Conclusions: This review serves as an essential resource for researchers in pharmaceutical sciences and drug discovery, highlighting the potential of natural bioactive molecules in circumvention of drug resistance. Leveraging nature's pharmacological arsenal may lead to more effective, safer, sustainable therapeutic strategies with reduced reliance on synthetic inhibitors that pose toxicological concerns, ultimately enhancing clinical outcomes in conditions associated with MDR.

1. Introduction

Multidrug resistance (MDR) remains a significant impediment to the effective clinical management of several illnesses. Several pivotal regulators are implicated in MDR, thereby compromising the effectiveness of treatment regimens. P-glycoprotein (P-gp), a 170-kilodalton integral membrane protein, is a key regulator, was first identified by Juliano and Ling in 1976 using colchicine-resistant Chinese hamster ovary cells. P-gp, with its widespread distribution in tissues, functions as a protective barrier, restricting the entry of foreign substances into the human body. While the protective function of P-gp is crucial in normal cellular physiology, its overactivity in cancer cells results in reduced cellular concentrations of chemotherapeutic drugs, limiting their effectiveness. Understanding the molecular mechanisms underlying P-gp-mediated drug resistance is crucial for formulating strategies to circumvent this phenomenon and enhance treatment outcomes. Medicinal herbs and spices have been recognized for their therapeutic benefits in a range of illnesses since antiquity and possess diverse pharmacological properties, including modulating the activity of drug transporter, P-gp. These natural botanicals are safe and have fewer adverse effects are easily accessible and are known to change the pharmacokinetics and pharmacodynamics of co-administered allopathic medicines and alter the toxicity

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patterns of these drugs. Inhibition of the phosphorylated glycoprotein by natural bioactive ingredients has been a promising method for overcoming drug resistance in tumour cells through coadministration with chemotherapeutics [1-4]. Given their minimal toxicity profile, identifying effective P-gp inhibitors has become a topic of increasing interest among contemporary researchers. In the context of chemical health risks, the modulation of P-gp also influences drug–herb interactions, bioavailability changes, and toxicity patterns, necessitating careful evaluation.

2. Objectives

This review aims to provide a scientifically curated overview of natural inhibitors of P-gp, elucidating their structural classes and mechanistic pathways in the context of MDR reversal.

3. Methods

A comprehensive search for publications on medicinal herbs, spices and bioactive compounds was conducted using online scientific databases, including Science Direct, PubMed and Google Scholar. This extensive global search focused on 100 commonly used medicinal herbs, 100 spices and 2129 bioactive components. The search criteria included studies on pharmacological properties and interactions of these compounds with P-gp (*in vivo*, *in silico* and *in vitro* studies). The integration of this diverse body of literature aimed to identify novel drug candidates and their relevance in treating the drug resistance mediated by P-gp in contemporary medicine.

4. Results

4.1 Pharmacological activity of natural bioactive compounds:

Therapeutic plants are rich in secondary metabolites, including alkaloids, flavonoids, coumarins, anthraquinones, lignans, saponins and terpenoids, which contribute to their bioactivity and determine their therapeutic effectiveness. These compounds exhibit diverse biological functions and their synergistic actions help protect the human body against a variety of diseases. Here, extensive research has identified natural bioactive substances derived from plants that suppress P-gp and counteract the MDR phenotype without undesirable toxic effects. The chemical structures are depicted in **Figure 1.**

4.1.1 Alkaloids

Alkaloids comprise a diverse class of phytochemicals derived from amino acids having a single or more basic nitrogen atom, usually arranged in a heterocyclic ring structure. Alkaloids are divided into various groups viz., tropane, indole, quinoline, purine, isoquinoline, imidazole alkaloids according to their heterocyclic ring system and precursor [5,6]. **Deoxypeganine,** a cholinesterase inhibitor from *Peganum harmala* is known to exert bronchodilator and abortifacient actions [7]. **Sanguinarine**, a benzophenanthridine alkaloid from *Chelidonium majus* induces cell cycle arrest and apoptotic cell death in human prostate carcinoma cells by affecting the machinery of cyclin kinase inhibitors, cyclins and cyclin-dependent kinases [8]. Quinoline alkaloids viz., **quinidine, dihydroquinidine** and **dihydroquinine** from *Cinchona pubescens* are used in the treatment of malaria [9]. **Reserpine**, an indole alkaloid from *Rauwolfia serpentina*, is known for its ability to lower blood pressure and has also been used as a tranquilizing agent [10]. **Tetrandrine**, a bisbenzylisoquinoline alkaloid derived from *Cissampelos pareira* and *Cyclea peltata* is recognized for its calcium channel blocking properties and shows efficacy in treating silicosis, hypertension, inflammation and lung cancer [11]. **Antofine**, a phenanthroindolizidine alkaloid, extracted from *Cynanchum paniculatum*, regulates the AKT/mTOR/AMP-activated protein kinase and ERK signalling pathways to control angiogenesis in cultured mouse embryonic stem cells and in human umbilical vein endothelial cells stimulated with vascular endothelial growth factor [12].

4.1.2 Flavonoids and Phenolics

A class of secondary metabolites known as flavonoids is composed of two aromatic rings and two benzene rings linked through three carbon atoms to form a heterocyclic structure. **Silymarin**, the active component of *Silybum marianum* is widely used for its neuroprotective, hepatoprotective, cardioprotective, antioxidant, anticancer, antidiabetic, antiviral, antihypertensive, immunomodulatory and detoxifying properties. It specifically targets several pathways, viz., Akt, mTOR, β-catenin and MAPK [13]. **Mangiferin** from *Swertia chirata* is known for its hypocholesterolemic, antiallergic, antidiabetic, neuroprotective, antioxidant and immunomodulatory properties [14]. **Karanjin** is a

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furanoflavonol derived from *Pongamia pinnata* with established antiglycaemic and gastroprotective effects [15].

4.1.3 Terpenoids

Terpenoids are a group of organic compounds composed of repeating C_5H_8 isoprene units. They play crucial role in various biological processes, including in the synthesis of essential oils, pigments, hormones, etc. They have been categorized as monoterpenoids ($C_{10}H_{16}$), sesquiterpenoids ($C_{15}H_{24}$), diterpenoids ($C_{20}H_{32}$), sesterterpenoids ($C_{25}H_{40}$), tetraterpenoids ($C_{40}H_{56}$) and triterpenoids ($C_{30}H_{48}$) [16]. **Keto-boswellic acid** is a triterpene derived from the gum resin of *Boswellia serrata* stems and has shown cytotoxic activity against triple-negative breast cancer cell lines *in vitro* [17]. **Oridonin** is a kaurene-type diterpenoid derived from *Rabdosia rubescens,* a potential anticancer agent which shows reversal of cisplatin resistance in human gastric cancer cell line [18].

4.1.4 Saponins, Sapogenins and Sterols

Saponins are glycosides composed of a sugar moiety attached to a hydrophobic aglycone known as sapogenin. The aglycone component contains a steroid or a triterpene, while the sugar moiety comprises of glucose, galactose, rhamnose, glucuronic acid, or xylose [19]. Triterpene saponins called bacopasides, extracted from *Bacopa monnieri*, suppress the proliferation of breast cancer cell lines such as ER-positive (T47D, MCF7) and HER2-positive BT-474 cells [20]. **Guggulsterone**, a phytosteroid extracted from the resin of *Commiphora wightii,* exhibits anticancer properties in gastric cancer SGC-7901 cells by inhibiting cell proliferation and stimulating apoptotic cell death [21].

4.1.5 Coumarins

Coumarin 1,2-benzopyrone (also known as 2H-1-benzopyran-2-one) and its derivatives are a group of crystalline, oxygenated heterocyclic compounds that are extensively distributed in plants either in free form or as heterosides. **Bergapten**, a furanocoumarin produced from *Ficus religiosa*, is considered as a potential drug candidate for treating diabetes, epilepsy, Alzheimer's disease, depression and cancer [22].

4.1.6 Miscellaneous natural inhibitors

There are additional active components that exhibit wide spectrum of medicinal properties including P-gp inhibitory activity like anthraquinones, lignans, tannins, lactones, etc. **Emodin**, an anthraquinone present in *Cassia fistula* and *Aloe barbadensis* exhibits neuroprotective, hepatoprotective, anti-inflammatory, immunosuppressive and muscle relaxant activities [23]. *Terminalia chebula* contains chebulagic acid, a benzopyran tannin that inhibits the AURKA/β-catenin/Wnt pathway, hence preventing stomach cancer [24]. **Hydnocarpin**, a flavonolignan from *Hydnocarpus wightiana* shows strong potential as a novel therapeutic candidate for acute lung injury, as it attenuates oxidative stress and inflammation induced by lipopolysaccharide through the MAPK/NF-κB and Keap1/Nrf2/HO-1 pathways [25]. **Dehydrocostus lactone**, a sesquiterpene lactone extracted from *Saussurea costus*, inhibits the proliferation of human myeloid leukemia cells through modulation of JAK/STAT signaling pathway [26].

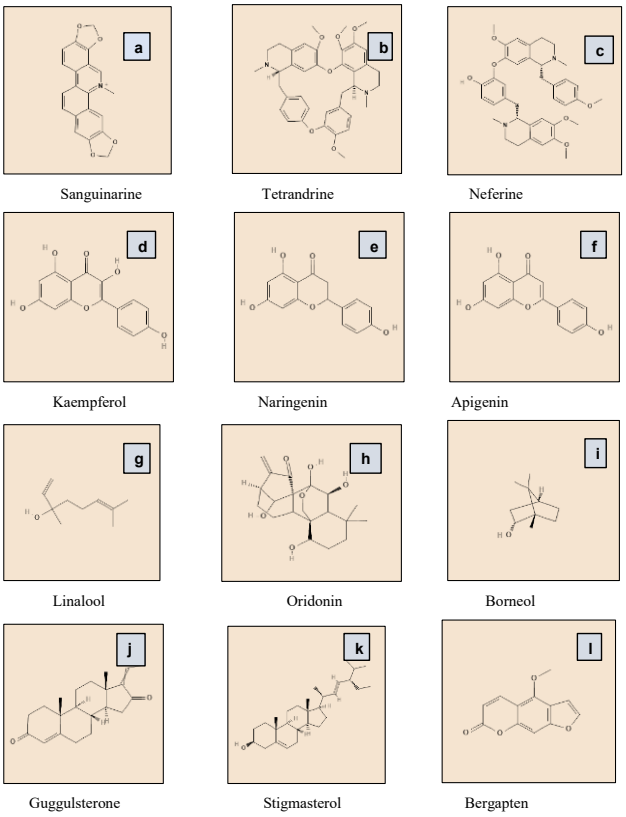

Figure 1: The structures of natural P-gp inhibitors

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4.2 Interaction of natural bioactive compounds with P-gp and its role in reversing chemoresistance:

Withaferin A, a steroidal lactone derived from *Withania somnifera*, functions as a potent NFκB inhibitor with well-established anticancer and radiosensitizing properties. Since NFκB hyperactivation and P-gp overexpression are major determinants of cancer chemoresistance, targeting NFκB represents an effective strategy to suppress MDR1 and restore chemosensitivity. In doxorubicin (DOX)-resistant K562/Adr leukemia cell, Withaferin A effectively suppresses NFκB activation, leading to decreased MDR1 expression. Unlike other NFκB inhibitors viz., quercetin or kaempferol, it can bypass P-gp-mediated efflux, triggering apoptosis even in resistant cells. Mechanistically, Withaferin A disrupts cytoskeletal organization by reducing tubulin levels and inducing vimentin aggregation, which promotes apoptosis through cytoskeletal destabilization. Moreover, its thiol-reactive α, β-unsaturated carbonyl group may interact with cysteine residues of P-gp, impairing its folding or transport activity. Overall, Withaferin A reverses MDR through dual action; inhibiting NFκB-driven MDR1 expression and directly interfering with P-gp function, thereby restoring drug sensitivity and enhancing chemotherapeutic efficacy [27].

Bergapten, a furanocoumarin compound found in *Ficus religiosa*, is a modulator of P-gp. Experimental studies using Caco-2 intestinal cell models demonstrated that bergapten significantly enhances the accumulation of [3H]-vinblastine, indicating direct inhibition of P-gp-mediated efflux [28].

Stigmasterol, a plant-derived phytosterol commonly found in citrus species and *Ficus religiosa*, has been identified as a natural modulator of P-gp. In MDR human leukemia (CEM/ADR5000) cells, stigmasterol, together with other bioactive compounds from *Citrus jambhiri* and *Citrus pyriformis*, was found to suppress P-gp–mediated export of the fluorescent substrate rhodamine 123, leading to increased intracellular substrate accumulation. Furthermore, treatment of P-gp–overexpressing Caco-2 and CEM/ADR5000 cells with stigmasterol enhanced DOX sensitivity, effectively reversing drug resistance [29].

Tannic acid, a polyphenol derived from *Ficus religiosa* and **penta-O-galloyl-ß-D-glucose** obtained from *Terminalia chebula*, shows inhibition of P-gp function in resistant KB-C2 cells. Both compounds markedly elevated the intracellular levels of substrates, including rhodamine 123 and daunorubicin, by inhibiting their efflux. At 60 μM and 100 μM, tannic acid and penta-O-galloyl-ß-D-glucose enhanced rhodamine 123 accumulation by 19- and 21-fold, respectively, far exceeding the effect of epigallocatechin gallate (EGCG). This inhibition was linked to decreased P-gp ATPase activity, indicating disruption of the ATP-driven transport mechanism. Mechanistic studies revealed that these polyphenols inhibit verapamil-induced ATPase activity, indicating suppression of the ATP hydrolysis required for P-gp transport function. The strong suppressive effect is attributed to the multiple galloyl groups in their structure, which enhance binding affinity to regulatory regions of P-gp [30].

Quercetin is a naturally occurring flavonoid obtained from *Ficus religiosa.* Experimental assays using calcein-AM and rhodamine 123 efflux shows that quercetin effectively blocks drug efflux, leading to increased intracellular accumulation of chemotherapeutic agents. Mechanistically, quercetin interferes with the transport cycle of P-gp, thereby preventing the conformational changes required for substrate translocation. This inhibition enhances the cytotoxic efficacy of drugs like paclitaxel, demonstrating its potential as a chemosensitizer for reversing P-gp–associated drug resistance in cancer therapy [31].

Myricetin, another flavonoid from *Ficus religiosa*, has been demonstrated to effectively suppress P-gp activity and improve the oral bioavailability of DOX. In MCF-7/ADR cells, myricetin significantly enhanced the level of rhodamine 123, indicating strong suppression of P-gp–mediated efflux. In *in vivo* pharmacokinetic studies, co-administration of myricetin with DOX in rats resulted in a 51–117% rise in the area under the concentration–time curve (AUC) and a 1.5–2.2-fold improvement in relative bioavailability, while intravenous pharmacokinetics remained unchanged. This selective enhancement of oral absorption suggests that myricetin primarily acts through intestinal P-gp inhibition, promoting increased drug uptake and systemic exposure [32].

Linalool, a monoterpene alcohol from *Alstonia scholaris*, shows MDR reversal in cancer cells. In studies

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using human breast adenocarcinoma cell lines (MCF7 WT and P-gp–overexpressing MCF7/AdrR), linalool significantly enhanced the anticancer efficacy of DOX. Additionally, it contributed to apoptotic induction by downregulating anti-apoptotic protein Bcl-xL, further amplifying DOX-induced cell death [33].

Terpinen-4-ol, the major bioactive constituent of *Alstonia scholaris* and *Boswellia serrata*, exhibits significant potential in targeting P-gp mediated MDR in cancer cells. In human melanoma M14 and adriamycin-resistant (M14/ADR) cell lines, terpinen-4-ol triggered apoptosis, with a stronger effect observed in the P-gp–overexpressing resistant cells. Mechanistic studies revealed that terpinen-4-ol interacts with the cell membrane, causing lipid reorganization that disrupts P-gp efflux function. This disruption enhances intracellular drug accumulation and restores apoptotic sensitivity in resistant cells [34].

Emodin, a natural anthraquinone derived from *Cassia fistula* and *Aloe barbadensis* shows P-gp inhibitory activity and reverse MDR in cancer cells. In P-gp–overexpressing chronic myelogenous leukemia K562/ADM cells, emodin significantly reduced P-gp protein expression and enhanced retention of rhodamine 123 and adriamycin, indicating suppression of drug efflux. Mechanistic analyses revealed that emodin binds preferentially to the R (rhodamine) site of P-gp with high affinity, acting as a competitive inhibitor that interferes with substrate transport [35].

Guggulsterone, a phytosteroid derived from *Commiphora wightii*, has demonstrated potent activity in reversing MDR in cancer cells. In DOX-resistant MCF-7/DOX breast cancer cells, co-treatment with guggulsterone (10 μM) markedly enhanced chemosensitivity to DOX, achieving a reversal effect comparable to that of the standard P-gp inhibitor verapamil. Mechanistically, guggulsterone increased the accumulation of rhodamine 123 and DOX, indicating strong suppression of efflux activity. This led to a substantial rise in apoptosis, with the apoptotic population increasing more than sixfold compared to DOX treatment alone [36].

Naringenin, a flavonoid from *Vitex negundo* and *Commiphora wightii*, functions as a potent modulator of P-gp and CYP3A4, two crucial determinants of drug transport and metabolism. In rat pharmacokinetic studies, co-administration of naringenin with the P-gp substrate felodipine significantly elevated its maximum plasma concentration (Cmax) and AUC in a dose-dependent fashion. The enhanced bioavailability of felodipine from 173.25 ng/mL to 275.61 ng/mL (single dose) and from 223.26 ng/mL to 561.32 ng/mL (multiple doses) at 100 mg/kg naringenin, indicates that it suppresses intestinal P-gp efflux, thereby improving drug absorption and retention. Supporting *in vitro* gut sac studies also demonstrated increased felodipine permeability in the presence of naringenin, comparable to the effects of the known P-gp inhibitor ritonavir. Mechanistically, naringenin interacts with P-gp by binding to its drug-binding pocket, thereby reducing ATPase-driven efflux activity. Concurrent CYP3A4 inhibition by naringenin minimizes metabolic degradation of felodipine, further elevating systemic exposure [37].

Chebulagic acid, a benzopyran tannin derived from *Terminalia chebula*, exhibits potent COX-2/5-LOX suppressive effect and demonstrates a remarkable capacity to modulate MDR in cancer cells. In *HepG2* hepatocellular carcinoma cells, co-treatment with chebulagic acid significantly enhanced the cytotoxicity of DOX, increasing its effectiveness nearly 20-fold. Chebulagic acid suppresses P-gp expression through a COX-2–dependent pathway. Prostaglandin E2 (PGE2), a COX-2 metabolite, is known to upregulate MDR1 expression, promoting drug efflux and resistance. Chebulagic acid inhibits COX-2 activity, thereby reducing PGE2 levels and downregulating MDR1 transcription, leading to reduced P-gp–mediated efflux of DOX. Additionally, it interferes with key signaling cascades, including Akt, ERK, JNK, p38 and NF-κB, thereby restoring drug sensitivity by diminishing P-gp expression and blocking its functional activity [38].

β-Sitosterol, a phytosterol from *Abies webbiana*, exhibits notable anticancer activity and modulates MDR. In comparative studies using estrogen-dependent (MCF7) and MDR (NCI/ADR-RES) breast cancer cells, β-sitosterol demonstrated higher cytotoxicity toward cells with basal ABCB1 expression while effectively inhibiting P-gp activity in resistant cells. Mechanistically, β-sitosterol interferes with P-gp–mediated ATP hydrolysis, impairing its transport function. Additionally, it induces G_0/G_1 cell cycle arrest and modulates cellular signaling pathways linked to

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proliferation and apoptosis. These combined effects contribute to sensitizing MDR cancer cells to chemotherapeutic drugs [39].

Tetrandrine, a bisbenzylisoquinoline alkaloid derived from *Cissampelos pareira*, has shown efficacy in counteracting drug resistance in cancer cells. In resistant colorectal cancer cell line and CEM/ADR5000 leukaemia cell, tetrandrine exhibited strong synergism with the chemotherapeutic agent DOX, significantly enhancing its cytotoxic effect. Mechanistic studies revealed that tetrandrine promotes higher intracellular level of rhodamine 123 through suppression of P-gp–mediated efflux. This inhibition leads to higher retention of anticancer drugs within resistant cells. Furthermore, tetrandrine downregulates expression of P-gp, indicating dual modulation at both functional and transcriptional levels [40].

Berberine, an isoquinoline alkaloid from *Cissampelos pareira* exhibits moderate inhibitory activity against P-gp at the blood–brain barrier (BBB). In cultured bovine brain capillary endothelial cells, berberine promotes greater intracellular retention of rhodamine 123, reflecting its ability to inhibit P-gp–mediated efflux [41].

Procyanidin, derived from *Saraca indica* and *Tamarindus indica*, shows strong potential in reversing drug resistance in cancer cells. In paclitaxel-resistant A2780/T ovarian cancer cells overexpressing MDR1, it markedly elevated the cytotoxic effects of paclitaxel and adriamycin by promoting higher intracellular drug retention and suppressing P-gp efflux activity. Mechanistic investigations revealed that it reduces P-gp level by suppressing MDR1 transcription. This effect is mediated through suppression of the NF-κB and ERK signaling pathways, which in turn prevent activation and nuclear movement of Y-box binding protein 1 (YB-1), a major transcriptional regulator of MDR1. It also prevents IκB breakdown and limits the nuclear translocation of NF-κB/p65, thereby further reducing P-gp expression [42].

In a separate study involving rat brain microvessel endothelial cells (RBMECs) and nude mice with human cerebroma, procyanidin was shown to elevate intracellular rhodamine 123 level in a dose-dependent fashion. At a concentration of 10 μM, it produced a fivefold increase in cellular rhodamine 123 level and blocked the ATPase activity of P-gp induced by verapamil by 78%, suggesting that it interferes with the ATP hydrolysis essential for drug efflux. This ATPase inhibition likely underlies its ability to suppress P-gp transport function. *In vivo*, co-treatment with procyanidin (80 mg/kg) alongside adriamycin (2 mg/kg) markedly improved therapeutic efficacy in tumor-bearing mice, extending survival by 76% [43].

Borneol, a bicyclic monoterpene from *Hemidesmus indicus*, *Sambucus ebulus, Salvia officinalis* has been effective in enhancing bioavailability of drugs by modulating P-gp activity. In experimental studies using isolated rat intestines and *in vivo* pharmacokinetic models, borneol increased the absorptive transport of colchicine and rhodamine 123, indicating inhibition of efflux activity of P-gp. Pharmacokinetic analysis further revealed that co-administration of borneol with colchicine led to a substantial rise in the highest plasma level (Cmax) and the corresponding AUC from 0 to 8 hours, confirming enhanced systemic exposure. Borneol interacts with the transmembrane domain of P-gp, thereby suppressing its ATP-dependent efflux function and facilitating greater drug permeability across the intestinal barrier [44].

Tetrahydropalmatine (THP), a major alkaloid component of *Tinospora cordifolia,* enhanced intracellular drug accumulation and potentiated the cytotoxicity of doxorubicin in P-gp-mediated MDR tumour cells. THP enantiomers reduced P-gp protein expression levels without significantly affecting mRNA expression, suggesting post-translational modulation of the transporter [45].

Palmatine, a protoberberine alkaloid from *Tinospora cordifolia* acts as a potential P-gp modulator. In an *in vivo* study using a metastatic breast cancer model, palmatine significantly inhibited lung colonization of breast cancer (4T1) cells. Treatment with palmatine (1–10 mg/kg) improved arterial oxygenation, reduced histological damage and decreased the expression of metastasis-associated protein 1 (MTA1) while enhancing the expression of the tumor suppressor p53. These effects collectively indicate attenuation of metastatic progression and cellular survival mechanisms [46].

Neochamaejasmin B (NCB), a biflavonoid from *Stellera chamaejasme*, exhibits strong P-gp

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inhibitory effect. In MDCK-hMDR1 cells, NCB enhanced intracellular rhodamine-123 level through dose-dependent inhibition of P-gp efflux, and this effect was supported by RT-PCR and Western blot evidence showing reduced P-gp expression. Kinetic and docking studies indicated a mixed type of inhibition, both competitive and non-competitive with high binding affinity toward P-gp [47].

Ferulic acid from *Artemisia japonica* enhances the antitumor activity of doxorubicin and vincristine in oral cancer KB ChR8-5 cells by modulating the NF-κB signaling pathway [48]. **Chelidonine, chelerythrine** and **sanguinarine,** alkaloids from *Chelidonium majus*, exert notable P-gp inhibitory effects. Chelidonine reverses DOX resistance in human colorectal adenocarcinoma and leukemia cells by inhibiting P-gp [49], while **chelerythrine** mitigates drug resistance in breast cancer cells by suppressing the expression of MDR1 and P-gp [50]. Sanguinarine reverses P-gp–mediated resistance by triggering apoptosis in CEM-VLB1000 leukemia cells [51]. **Linolenic acid** from *Ipomoea aquatica* downregulates P-gp expression, enhancing intracellular level of DOX and rhodamine 123 in K562/ADM cells [52]. **Neferine**, a bisbenzylisoquinoline alkaloid from *Nelumbo nucifera*, enhances rhodamine 123 uptake in paclitaxel-resistant and DOX-resistant cancer cells, including MCF-7, A549, and HCT8 [53]. **Reserpine**, an indole alkaloid from *Rauwolfia serpentina*, increases DOX uptake in P-gp–overexpressing cells [54], while **hydnocarpin** from *Hydnocarpus wightiana* potentiates vincristine cytotoxicity in acute lymphoblastic leukemia cells [55].

Mollugin derived from *Rubia cordifolia* lowers P-gp expression by inhibiting NF-κB signaling and COX-2, and further suppresses CRE-mediated transcription through the activation of AMPK [56]. **Mangiferin** from *Swertia chirata* inhibits P-gp activity in HK-2 proximal tubule and vincristine-resistant Caco-2 cells [57], whereas **syringaresinol** from the same plant suppresses P-gp in adriamycin-resistant MCF-7 breast cancer cells [58]. **3-O-acetyl-11-keto-boswellic acid** derived from *Boswellia serrata* reduces P-gp transport activity in human lymphocytic leukemia and porcine brain capillary endothelial cells [59]. **Bacopaside I** from *Bacopa monniera* inhibits the translocation of rhodamine 123 across LLC-GA5-COL150 cell monolayers [60]. **Quercetin-3-rhamnoside** from *Actinodaphne hookeri* enhances pirarubicin cytotoxicity in erythromyelogenous leukemic, K562/Adr and Glc4/Adr cells through non-competitive inhibition of P-gp and MRP1 [61]. **Cynarin** from *Tanacetum parthenium* increases DOX accumulation in uterine sarcoma MES-SA/Dx5 cells [62]. **Paeonol** from *Cynanchum paniculatum* overcomes paclitaxel resistance in breast cancer cells by modulating expression of transgelin 2 [63]. **Cinchonine** and **quinidine** from *Cinchona pubescens* enhances the cytotoxic effects of paclitaxel in MES-SA/Dx5 uterine sarcoma cells [64]. **Stemofoline** from *Stemona aphylla* shows P-gp reversal effect in KB-V1 nasopharyngeal carcinoma cells, increasing sensitivity to paclitaxel, vinblastine, and doxorubicin [65]. **Silymarin** from *Silybum marianum* promotes daunomycin and doxorubicin retention in cancer cells [66], while **morin** from *Bergenia ciliata* suppresses P-gp activity by inhibiting its photoaffinity labeling with [(^{3})H] azidopine [67].

Karanjin from *Pongamia pinnata* inhibits ABCB1-mediated efflux of drugs in UKF-NB-3 and UKF-NB-3(r)VCR^{10} cells [15]. **Obacunone** from *Phellodendron amurense* exhibits inhibition of drug resistance in uterine sarcoma and human colon cancer cell lines [68]. **3,3′,4′,5,7-pentahydroxyflavone** from *Mimusops elengi* suppresses P-gp expression in both the small intestine and liver of rats [69]. **Dehydrocostus lactone** from *Saussurea costus* downregulates ABCB1 expression in liposarcoma and synovial sarcoma cells and induces apoptosis, as evidenced by enhanced activation of caspase-3/7 along with caspase-3 and poly (ADP-ribose) polymerase cleavage [70]. **Baicalein** from *Terminalia arjuna* reduces P-gp expression in rat gut sacs and human colorectal adenocarcinoma cells, leading to increased rhodamine 123 accumulation [71]. **Uvaol** from *Nerium odorum* inhibits rhodamine 123 efflux in resistant mouse lymphoma cells [72]. **Wogonin** from *Guaiacum officinale* enhances etoposide-triggered apoptosis in HL-60 cells [73]. **Deoxypeganine** from *Peganum harmala* downregulates MDR expression in L5178Y mouse lymphoma cells [74]. **Ellagic acid** from *Terminalia chebula, Commiphora wightii, Phyllanthus emblica, Emblica officinalis* increases the bioavailability of diltiazem [75] and linagliptin [76] in male Wistar rats by suppression of P-gp. **Aconitine, mesaconitine**, and **hypaconitine**, the active alkaloids from *Aconitum heterophyllum* counteracts drug efflux in Caco-2 cells,

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enhancing their apical-to-basolateral transport and overall intestinal absorption [77]. **Rutaecarpine** and **evodiamine** from *Evodia elleryana* exhibit P-gp modulatory activity in CCRF-CEM leukemia cells and their P-gp overexpressing subline CEM/ADR5000 [78]. **Epigallocatechin-3-gallate** from *Cissampelos pareira* and *Nigella sativa* downregulates P-gp expression in tamoxifen-resistant MCF-7 breast cancer cells while promoting the accumulation of rhodamine 123 and calcein-AM in Caco-2 cells [79]. **Piperine** from *Piper nigrum* reverses MDR in KB and SW480 cancer cells when co-administered with vincristine or paclitaxel [80]. **Curcumin** and its derivatives, **α- and aromatic turmerones** from *Curcuma longa*, inhibit rhodamine-123 efflux [81] and suppress expression of MDR1 mRNA in Caco-2 cells [82]. **Apigenin** from *Apium graveolens* reverses drug resistance in MCF-7/ADR cells by suppressing the STAT3 signaling pathway [83]. **Caffeic acid** from *Tanacetum parthenium* and *Apium graveolens* inhibits rhodamine 123 efflux uncompetitively and DOX efflux competitively [84]. **6-Gingerol** from *Zingiber officinale* enhances intracellular rhodamine 123 and daunorubicin accumulation in KB-C2 cells [85], while **kaempferol** from *Cassia fistula* and *Prunus dulcis* decreases P-gp expression in the immortalized proximal tubular cell line HK-2 [86] and reduces vinblastine and paclitaxel resistance in KB-V1 cells [87]. **Gallic acid** from *Terminalia chebula* and *Origanum majorana* enhances the oral bioavailability of linagliptin in male Wistar albino rats [88]. **Sesamin, sesamolin**, and **sesamol** from *Sesamum indicum* increase rhodamine 123 accumulation in LS-180V cells [89] and elevate its intracellular concentration by 1.6–1.8-fold in R-HepG2 cells [90]. **Rutin** from *Allium sativum* reduces expression of P-gp in KB CHR 8-5 cell lines [31], while **β-caryophyllene** from *Curcuma longa* potentiates the cytotoxicity of doxorubicin in HepG2 cells [91]. **Chlorogenic acid** from *Withania somnifera* and *Apium graveolens* exhibits P-gp inhibitory activity in rat jejunal membranes [92], while **citronellol**, a monoterpenoid derived from *Nigella sativa*, enhances the intracellular retention of [^{3}H] digoxin in MDR1-transfected LLC-GA5-COL150 cells, demonstrating its potential to block P-gp–mediated drug export [93].

Therefore, these phytochemicals act through diverse mechanisms such as downregulating P-gp expression, blocking efflux activity and modulating key signaling pathways ultimately enhancing intracellular drug retention and reversing MDR in cancer and related diseases.

4.3 Molecular Interactions and Binding Residues

Molecular interaction analysis provides valuable insight into the binding behavior of natural bioactive compounds with P-gp (**Table 1**).

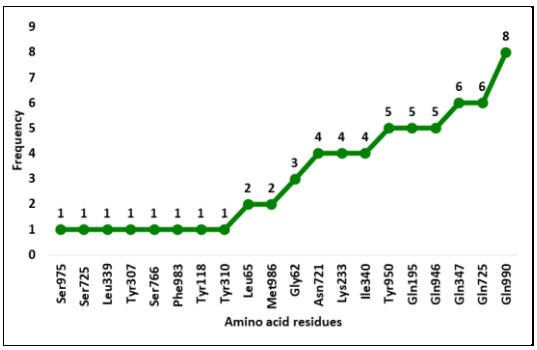

Figure 2: The figure represents the frequency of amino acid residues involved in hydrogen bonding between bioactive components and P-gp

Figure 2 depicts the frequency distribution of amino acid residues involved in hydrogen bonding between bioactive components and P-gp. Gln990 (13.11%) exhibits the highest frequency, suggesting its crucial role in hydrogen bonding with epigallocatechin, epigallocatechin gallate, tamarixetin, morin, pelargonidin and hesperidin. Gln725 (curcumin, epigallocatechin gallate, proanthocyanidin, morin, pelargonidin) and Gln347 (hesperidin) (9.84%) also play significant roles in stabilizing interactions via hydrogen bonds. Gln946 and Gln195 (8.20%) further contribute to hydrogen bonding with hesperidin and tamarixetin. Lys233 (oleic acid, linoleic acid, octadecanoic acid), Tyr950 (rutin, theaflavine, tamarixetin, hesperidin), Asn721 (quercetin, curcumin, proanthocyanidin) and Ile340 (isoquercitrin, rutin, epicatechin 3-gallate) participate in hydrogen bonding but at a lower frequency (6.56%) compared to glutamine-rich residues. Gly62 (rutin, theaflavine) (4.92%), Met986 (tamarixetin, proanthocyanidin) (3.28%), Leu65 (rutin) (3.28%) show lower involvement, indicating secondary roles in hydrogen bonding. Minor contributions come from Tyr118 (epicatechin 3-gallate), Tyr310 (epigallocatechin gallate), Phe983 (isoquercitrin), Ser766 (quercetin), Tyr307 (pelargonidin), Leu339 (proanthocyanidin) and Ser725 (baicalein) (each ≤1.64%).

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The prevalence of glutamine-rich binding sites suggests that these residues serve as key hydrogen-bonding hotspots, which could be targeted for drug design. Enhancing interactions with these residues may improve drug binding affinity and stability within P-gp. Understanding hydrogen bonding hotspots is critical for developing bioactive compounds that can effectively modulate P-gp function, particularly in overcoming MDR.

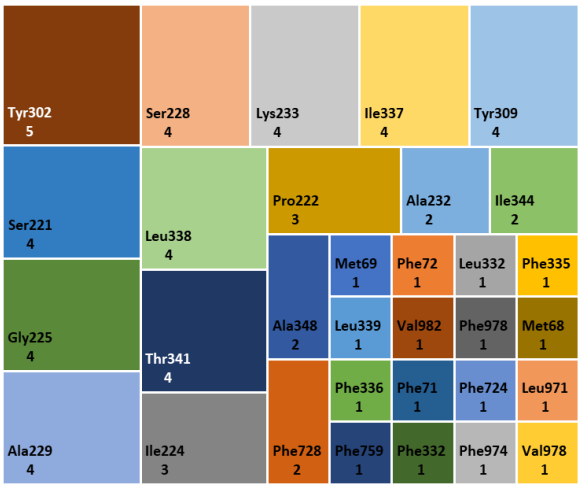

Figure 3: The tree map represents the frequency of amino acid residues engaged in hydrophobic interactions between bioactive components and P-gp

Figure 3 depicts the frequency of amino acid residues engaged in hydrophobic interactions between bioactive components and P-gp. Tyr302 (7.14%) shows the highest frequency, indicating its major role in hydrophobic interactions with oleic acid, linoleic acid and octadecanoic acid. Several residues viz., Thr341, Leu338, Tyr309, Ile337, Lys233, Ser228, Ala229, Gly225 (each at 5.71%) also play a significant role in these interactions. Ser221 (octadecanoic acid, oleic acid, linoleic acid), Pro222, Ile224, Ala232 (oleic acid, linoleic acid), Ala348 (octadecanoic acid, linoleic acid), Ile344 (octadecanoic acid), Phe728 (baicalein) contribute moderately (2.86% - 4.29%) to hydrophobic interactions. Phe72, Leu332, Phe335, Leu339, Phe336, Phe759, Phe978, Val982 (boeravinone B), Phe71, Phe332, Phe724, Leu971, Phe974, Val978 (baicalein) have lower frequencies (≤1.43% - 2.86%), indicating limited but still relevant hydrophobic interactions.

Nonpolar residues viz., Tyr, Phe, Leu, Ile, Val and Met are commonly found in lipophilic binding pockets, favouring interactions with hydrophobic molecules. Identifying these hydrophobic hotspots is valuable for designing P-gp inhibitors that can effectively engage these binding pockets. Since hydrophobic interactions are crucial for drug affinity, modifying compounds to enhance their interactions with these residues may improve their inhibitory potential.

Table 1. Binding Interaction of Natural Bioactive Compounds.

Name of herbs and spices	Bioactive compounds	Binding interactions (*in silico*)
Ficus religiosa	Myricetin	Shows hydrogen bond interactions with Ile-306, Asn-721(homology modeled human P-gp from mice) [32].
Cassia fistula	Linoleic acid	Shows interactions with Ser221, Ile224, Pro222, Gly225, Ala229, Ser228, Lys233, Tyr309, Tyr302, Leu338, Ile337, Ile344, Thr341, Ala348 (hydrophobic) and Lys233(hydrogen) (homology modeled rat P-gp) [94].
Boerhavia diffusa	Boeravinone B	Participates in hydrophobic interactions involving Met69, Phe72, Leu332, Phe335, Leu339, Phe336, Phe759, Phe728, Val982, Phe978 of homology modeled human P-gp [31].
Hemidesmus indicus, Allium sativum	Rutin	Exhibits hydrogen bonding with Gln347, Gly62, Gln195, Ile340, Leu65, Tyr950, Gln946 (homology modeled human P-gp from mice) [31].
Pterocarpus marsupium	Octadecanoic acid	Shows interactions with Ser221, Gly225, Ala229, Ser228, Lys233, Tyr309, Tyr302, Ile337, Leu338, Thr341, Ala348, Ile344 (hydrophobic) and Lys233(H) (homology modeled rat P-gp) [94].
Cocculus pendulus, Nigella sativa	Oleic acid	Shows hydrophobic interactions with Ser221, Ile224, Pro222, Gly225, Ala229, Ser228, Ala232, Tyr302, Lys233, Tyr309, Leu338, Ile337, Thr341 and one hydrogen bond with Lys233 (homology modeled rat P-gp) [59].
Terminalia arjuna	Baicalein	Exhibits three hydrogen bonds with Ser975 and Ser725 residues and Van der Waals interaction with Met68, Phe71, Phe332, Phe724, Phe728, Leu971, Phe974, Val978 (*Mus musculus*) [95].
Vitex negundo, Brassica nigra, Sinapis nigra	Myricetin	Shows hydrogen bonding with Ile-306, Asn-721(homology modeled human P-gp from mice) [32].
Allium sativum	Quercetin	Involved in hydrogen bonding with Asn-721, Ser-766 (homology modeled human P-gp from mice) [31].
Carum carvi	Isoquercitrin, Theaflavine, Epicatechin 3-gallate	Isoquercitrin shows hydrogen bond interaction with Gln-347, Ile-340, Phe-983, theaflavine shows interactions with Gln-725, Tyr-950, Gly-62, epicatechin 3-gallate interacts with Gln-347, Ile-340, Tyr-118 (homology modeled human P-gp from mice) [31].
Curcuma longa	Curcumin, Epigallocatechin, Epigallocatechin gallate, Tamarixetin	Curcumin shows hydrogen bond interaction with Gln-725, Asn-721, epigallocatechin interacts with Gln-990, Gln-990, epigallocatechin gallate depicts interactions with Gln-725, Gln-990, Tyr-310, tamarixetin shows interactions with Gln-195, Gln-946, Met-986, Gln-990, Gln-990, Tyr-950 (homology modeled human P-gp from mice) [31].
Theobroma cacao	Proanthocyanidin, Morin, Pelargonidin, Hesperidin	Proanthocyanidin shows hydrogen bond interaction with Asn-721, Asn-721, Gln-725, Met-986, Leu-339, morin depicts interactions with Gln-990, Gln-725, pelargonidin interacts with Tyr-307, Gln-725, Gln-990, hesperidin shows interactions with Gln-990, Gln-347, Gln-347, Gln-195, Gln-195, Gln-946, Gln-946, Tyr-950 (homology modeled human P-gp from mice) [31].
Aconitum heterophyllum	Atisine, kutkin	Atisine shows two hydrogen bonds with Ser979, Glu972 and six hydrophobic interactions with Phe72, Phe336, Leu332, Leu975, Leu976, Ile736, kutkin depicts hydrophobic interactions with Phe336, Phe732, Phe72, Leu975, Leu976, Ile736 (human P-gp, 6C0V) [96].
Rauwolfia serpentina	Deserpidine, ajmalicine	Deserpidine shows hydrogen bonding with Leu332, Glu972, Leu975, Thr76, Ser979 and eight hydrophobic interactions with Phe72, Phe79, Phe732, Leu332, Leu975, Leu976, Ile736, Ile328, ajmalicine engages in hydrogen bond formation with Glu972 and exhibits three hydrophobic interactions with residues Leu332, Leu976, Ile736 (human P-gp, 6C0V) [97].
Pandanus odoratissimus	Pandamarilactone -31	Shows hydrogen bond with Ser733, Gly737, Glu972 and exhibits hydrophobic contacts involving Phe72, Leu332, Phe732 (human P-gp, 6C0V) [98].

5. Discussion

Multidrug resistance poses a significant challenge in modern medicine, particularly in cancer treatment. P-gp, an ATP-driven membrane transporter, contributes significantly to MDR by actively exporting chemotherapeutic agents from cells. The overexpression of P-gp in cancer cells severely limits intracellular drug accumulation and necessitates higher therapeutic doses, thereby amplifying systemic toxicity and chemical health

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risks. Therefore, modulation of P-gp activity has emerged as a strategic approach to restore drug sensitivity, reducing toxic exposure and mitigating risk to human health.

Natural compounds from medicinal plants have drawn considerable attention as potential P-gp inhibitors due to their structural diversity, pharmacological safety and accessibility. This review provides a comprehensive overview of 100 natural P-gp inhibitors, detailing their underlying mechanisms and potential for overcoming drug resistance. The identified compounds belong to various classes, including alkaloids, flavonoids, terpenoids, saponins and phenolics, each possessing unique structures and properties. These phytoconstituents exert their modulatory effects either by directly binding to the transmembrane domain of P-gp, thereby inhibiting substrate efflux, or by suppressing its expression at the transcriptional and translational levels. Furthermore, these natural inhibitors can augment the intracellular concentration of chemotherapeutic medications, thereby improving their cytotoxic effects against resistant cancer cells.

Furthermore, mechanistic insights indicate that certain compounds, viz., withaferin A, guggulsterone and chebulagic acid, act through dual pathways, both inhibiting NFκB-mediated MDR1 expression and interfering with ATPase-driven transport functions. Flavonoids viz., quercetin, myricetin and naringenin exhibit synergistic effects when co-administered with conventional chemotherapeutics, thereby enhancing oral bioavailability and cytotoxic potency. Similarly, terpenoids and saponins viz., linalool, terpinen-4-ol and bacopasides demonstrate membrane-disruptive and signaling-modulatory effects that contribute to MDR reversal. Therefore, the combinatorial potential of these natural inhibitors with existing drugs could be harnessed to design multi-targeted treatment regimens that overcome the limitations of synthetic P-gp inhibitors, which often suffer from toxicity and pharmacokinetic instability.

The structural complexity of these phytochemicals also provides a unique platform for rational drug design and semi-synthetic optimization. Computational docking and molecular dynamic studies have revealed critical binding interactions between natural inhibitors and key residues of P-gp, viz., Phe336, Leu332, Ser979 and Glu972. These findings thus offer valuable insights into the molecular basis of inhibition and can guide the development of more potent derivatives with improved specificity and stability. Moreover, integrating natural inhibitors into nanoformulations or targeted delivery systems may enhance bioavailability and stability, thereby reducing off-target toxicity and achieve controlled modulation of P-gp function.

6. Conclusion

This review, therefore, emphasizes that medicinal plants represent a rich and largely untapped reservoir of natural compounds capable of modulating P-gp activity and counteracting MDR. By leveraging these bioactive molecules through structural optimization and combinatorial therapeutic approaches, pharmaceutical strategies against MDR can be significantly improved. Further research is essential to elucidate their pharmacokinetic behavior, bioavailability and potential adverse effects to enable their successful clinical translation. Additionally, semi-synthetic modification of these natural scaffolds may yield next-generation P-gp inhibitors with enhanced potency, selectivity and safety profiles.

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