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SYNERGY IN PHYTOTHERAPY

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ABSTRACT
Drugs obtained from natural resources account for a larger portion of the pharmaceutical industry. The effective traditional use of herbal medication combinations necessitates to find the basis for their therapeutic advantages over individual ingredients. Synergistic interactions play a crucial role in phytomedicines, explaining both the challenges associated with consistently identifying a single active component and the effectiveness of apparently tiny concentrations of active ingredients in herbal products. Since adjuvant compounds found in plants can increase the action of the active components, it is necessary to re-evaluate the notion that medications produced from plants are dependent on active principles. This synergy may include preventing an active ingredient from being broken down by enzymes, facilitating transport through obstacles like cell and walls of organelle, overcoming mechanisms of multi-drug resistance, or even sending additional signals that increase the efficacy of the bioactive compounds in comparison to its isolated components. Also, real synergistic effects may be verified by way of controlled clinical trials conducted in comparison to conventional reference medications, as well as thorough pharmacological research. Many new researches that is now underway aims to generate a new range of phytomedicines that could be used separately or in conjunction with synthetic medications or antibiotics. This review examines the number of studies that suggests phytotherapy can work in synergy including the ways to assess this synergy.

Keywords: *phytotherapy, phytomedicine, synergy, herbal medicine, natural products, pharmacokinetic, pharmacodynamics, interactions.*

INTRODUCTION
Throughout history, plants have been integral to human existence, serving as sources of sustenance, shelter, medicine, flavour, fragrance, textiles, and fertilizers. Ancient civilizations, including the Sumerians, Indians, Chinese, Egyptians, and Latin Americans, documented the use of herbal mixtures for healing [1]. Today, a substantial global population continues to rely on natural herbal remedies and supplements for basic healthcare [2]. Indigenous healers, across generations, have harnessed plant materials and purified constituents to treat a variety of ailments [3.4]. These natural products are valued for their unique qualities, including effectiveness, safety, and minimal side effects. Plant-derived bioactive compounds, known for their multifaceted effects such as antioxidative, anticancer, immunostimulatory, anti-inflammatory, and antimicrobial properties, play a vital role in maintaining human health [5,6]. Plants contain a diverse array of chemicals, such as alkaloids, terpenoids, coumarins, flavonoids, and more, with wide-ranging bioactivities like anti-inflammatory, anti-cancer, antioxidant, and antibacterial effects [3]. Some commonly used medicinal plants include Chamomile, Peppermint, Holy Basil, neem, turmeric, aloe vera, and many others. Traditional medicine, developed over generations, draws on indigenous wisdom, theories, beliefs, and experiences, whether explainable or not, to preserve health and address physical and mental illnesses [7]. Modern scientific tools, like microscopes and chemical analysis, have allowed for the isolation of active constituents within medicinal plants [8]. While traditional herbal practices have evolved into the pharmaceutical industry, plant-derived compounds remain essential in many medications [9]. Despite advances in synthetic alternatives, traditional plant-based medicine remains cost-effective and widely used in developing countries. This enduring reliance underscores the enduring significance of plants in modern healthcare.

Phytotherapy, also known as herbalism in Western medicine, is a practice that employs plants to treat ailments and promote well-being. Traditional phytotherapies often maintain the natural composition and integrity of the parent plant, using the whole plant or specific unaltered components for therapeutic purposes. Various medical traditions, including traditional Chinese medicine (TCM), naturopathic medicine, anthroposophic medicine, and Ayurvedic medicine, rely on plant-based therapies. Practitioners may prescribe individual herbs, combinations of plants with complementary effects, or mixtures of herbs and non-herbal substances like minerals and vitamins. While Western herbal medicine often employs standardized extracts from single herbs, traditional phytotherapy frequently utilizes the entire plant, such as brewing chamomile herb infusions (tea). In contrast,

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pharmaceutical drugs derived from plants often consist of isolated single molecules, industrially extracted from parts found to possess therapeutic qualities [10].

Despite the expansion of the healthcare industry in the wake of the Industrial Revolution, phytotherapy remains a viable and effective treatment option. For example, Aristolochia cymbifera extracts combat diseases and multi-resistant Staphylococcus aureus (MRSA). While some Aristolochia paucinervis species have health concerns, they also have antibacterial properties. Other plants like Myrospermum erythroxylon, Bathysa cuspidata, Cosmos sulphureus, Cecropia hololeuca, and Prasia lactescens can combat bacterial strains effectively. However, concerns regarding the safety of phytotherapeutic drugs have led to misinformation [11].

Plants serve as sources of essential drugs like atropine, scopolamine, morphine, codeine, digoxin, and curare, often used in teas, homemade preparations, paints, powders, tablets, capsules, and extracts [12]. Bioactive compounds are extracted through a process involving extraction, separation, and purification, leading to the term "phytomedicine" [13]. A key distinction must be made between "medicinal plants" and "phytomedicines" or "phytotherapeutics." The latter undergoes strict production procedures from collection to distribution and adheres to ethical criteria established by the World Health Organization (WHO). Consistent processing of source plant materials is necessary to ensure the final product contains a standardized marker ingredient at a validated concentration. Given the variety of chemical compounds in plants, the finished product is standardized to this marker ingredient. This precision is essential for delivering the active ingredient at a therapeutically effective dosage in therapy [10].

Synergy, a fundamental natural principle, encapsulates the notion that "the whole is greater than the sum of its parts," as Aristotle advocated [14]. While widely acknowledged, it's important to note that synergy doesn't always result in superior or positive outcomes. In the realm of pharmacology, a notable shift has occurred towards combining drugs. This approach has substantially improved the treatment of various conditions, including AIDS and cancer [15)]. Furthermore, there's a growing trend in therapies that focus on activating the body's natural protective mechanisms, especially in the context of plant extracts, where intricate interactions are abundant [16]. To evaluate and understand synergy, various mathematical methods are employed. These methods vary, with some offering qualitative insights (like the isobologram), while others provide quantitative measures of interaction intensity (such as the response surface method) [17,18]. The choice of method often depends on computational requirements and the desired level of precision, contributing to the diversity in synergy research methodologies.

Synergy research in Phytomedicine has emerged as a vital field. It aims to scientifically justify the therapeutic superiority of traditional herbal drug extracts over single components. Clinical studies confirm the effectiveness of these plant extracts, often attributed to synergy among bioactive constituents. Understanding these mechanisms is crucial for developing standardized, effective mono- and multi-extract preparations that meet modern standards, potentially replacing chemosynthetics and antibiotics for certain conditions. This research is prompted by pharmaceutical legislation's demand for complete efficacy verification in combined pharmaceutical preparations [19].

HISTORICAL CONTEXT

Natural ingredients have always offered an infinite supply of medication. For thousands of years, practically without opposition, products derived from plants have ruled the human pharmacopoeia [20]. Aspirin (acetylsalicylic acid), the first synthetic medicine, was developed in 1897 by Arthur Eichengrün and Felix Hoffmann using salicylic acid, an active component of plant analgesics. This marked the milestone in the history when the pharmaceutical industry prevailed. Recent advancements in combinatorial chemistry, computer (in silico) drug design, and structure activity-based organic synthesis have reduced the importance of naturally occurring substances derived from plants in drug development.

Plants and other biological sources continue to be an unabated supply of novel medicines, despite drug discovery technological diversity and decreased funding for natural product drug development. Since 1984 to 2003, industrial support for the development of drugs based on natural products has been falling, while the proportion of small molecules with natural product origins has been mostly stable [21]. According to a thorough analysis of all human medications approved since 1981, of the 847 small molecule-based medications, 43 were generated naturally, 232 were generally semi-synthetically made from natural materials, and 572 were made from synthetic molecules. But, 262 out of 572 synthesised exhibited pharmacophores that were either driven by natural products and may be regarded as natural product analogues. The greatest notable impact is still being made by herbal products in the fight against cancer. Only 27% of the 155 antitumor medications created during the 1940s could not be linked to natural sources, with 47% constituting either a natural source or a direct

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derivative of one. The anticancer agent sorafenib was the only medication that could be fully attributed to de novo combinatorial chemistry [22]. Biologics and vaccinations, which are drawn from nature, were not included in the study above.

The Evolution of Medicinal Plant Use: From Ancient Civilizations to Modern Pharmaceuticals

Medicinal plant use boasts a rich history, spanning millennia, from its earliest mentions in ancient texts to contemporary pharmaceutical breakthroughs.

Ancient Roots (Before 3000 B.C.): The history of medicinal plants begins in prehistoric times, around 3000 B.C., with the discovery of the Ice-man, carrying herbs, a testament to early plant-based healing practices. As human civilization progressed, so did the documentation of herbal knowledge.

Ancient Civilizations (3000 B.C. - 200 A.D.): Around 3000 B.C., Sumerians started documenting medicinal plant use, setting the stage for a systematic understanding of herbal remedies. By around 2700 B.C., Chinese Emperor Shen Nung authored the "Pen T-Sao," cataloging medicinal plants and their uses, a pivotal contribution to herbal medicine.

Ancient Wisdom and Writing (1700 B.C. - 1500 B.C.): Around 1700 B.C., the Law Code of Hammurabi mentioned many medicinal plants in Mesopotamia, emphasizing the integration of herbal remedies into legal and healthcare systems. Roughly 1500 B.C., the Eber's Papyrus from Egypt contained numerous herbal prescriptions, underlining the significance of written knowledge in preserving herbal wisdom.

Indian Ayurveda and Greek Influence (1000 B.C. - 100 B.C.): By 1000 B.C., Indian Ayurvedic texts recorded diverse herbal remedies, enriching global botanical knowledge. In 340 B.C., the Greek philosopher Theophrastus authored pivotal works on medicinal plant uses and cultivation. A century later, in 100 B.C., Krateus, a Greek herbalist, published the first illustrated book on medicinal plants, making herbal knowledge more accessible.

Roman Contributions (60 A.D. - 78 A.D.): In 60 A.D., Pliny wrote "Natural History," detailing over 1000 plant species and their medicinal uses. In 78 A.D., Dioscorides documented herbal drug collection and usage in "De Materia Medica," a classic text.

Chinese and Oriental Traditions (200 A.D. - 800 A.D.): Around 200 A.D., Chang Chung-Ching laid the foundation for Chinese and Oriental herbal medicines with his foundational works. By 800 A.D., the Arab world had established private drug stores, becoming purveyors of diverse herbal remedies, highlighting the global reach of herbal knowledge.

Medieval Herbalists and European Monasteries (800 A.D. - 1240 A.D.): Around 1000 A.D., Ibn Sina (Avicenna) penned Arabic texts on healing and herbal medicines, continuing to influence herbal knowledge for centuries. Around 1240 A.D., Ibn al-Baytar, a renowned herbalist in medieval Spain, described over 1000 botanical medicines. European monasteries from 500-1200 A.D. played a critical role in preserving herbal wisdom.

Transition to Modern Medicine (17th - 19th Century): The 17th century marked the introduction of Cinchona bark from the New World for malaria treatment in 1640 A.D. In 1785 A.D., William Withering's discovery of the medicinal properties of Digitalis purpurea marked the shift from traditional herbal remedies to modern pharmacology. In 1795 A.D., the British Navy provided lemon juice to prevent scurvy, emphasizing the connection between nutrition and health. The 19th century saw pivotal developments. In 1803 A.D., Wilhelm Serturner isolated morphine and alkaloids, ushering in the era of alkaloid-based medications. In 1820 A.D., P-J. Pelletier and J.-B. Caventou isolated quinine, emetine, strychnine, and brucine. In 1838 A.D., Raffaele Piria isolated salicylic acid from willow bark. In 1897 A.D., Bayer synthesized aspirin, marking the birth of the modern pharmaceutical industry.

Modern Discoveries and Regulations (20th and 21st Century): In the 20th century, discoveries abounded. In 1971 A.D., the US National Cancer Institute uncovered Taxol® from Taxus brevifolia. In 1978 A.D., Germany established Commission E monographs for herbal medicines, setting standards. In 1984 A.D., the National Cancer Institute endorsed dietary fiber's benefits. In 1988 A.D., K. During and A. Hiatt produced human antibodies in tobacco plants. In 1992 A.D., the Convention on Biological Diversity (CBD) was established. In 1994 A.D., the Dietary Supplement Health and Education Act (DSHEA) legitimized the nutraceutical industry. In 1997 A.D., the US FDA approved the first food-specific health claim. Around 2000 A.D., pharmaceutical companies shifted focus. In 2000 A.D., the US FDA issued Botanical Drug guidance. In 2001 A.D., the FDA allowed the sale of galanthamine. In 2003 A.D., the FDA issued the "Guidance for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements." (Raskin & Ripoll, 2004).

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MECHANISM OF ACTION

The function of certain medicinal plants may now be explained rationally thanks to advances in fundamental cell molecular biochemistry and the potential to clarify pharmacological mechanisms of action at the cellular or even gene level. Thus, the mechanism of action and appropriate dose of the conventionally used crude extracts may be compared with those of their separated or synthesised equivalents. It turns out—quite surprisingly—that the separated material is frequently less active when taken out of its natural context and instead remains in the combination seen in the plant. Cott and Misra [23] observed that within the field of psychotherapy plants, compounds extracted from *Hypericum perforatum*, *Passiflora incarnata*, and *Rauwolfia serpentina* did not replicate the action of the crude extracts. It was clear that a synergistic effect was at work, wherein some medicinally inert components of the plants might augment the action of the so-called active principles and, in certain situations, as with *Rauwolfia*, lessen the toxicity associated with the extracted active principle. The isolated active principle artemisinine, when administered orally to humans at a total dose of 3000 mg over 4 days, produces a result in terms of parasitemia, fever abatement, and recrudescence rate that is not significantly better than that obtained in a four-day course of leaf tea, which corresponds to a total dose of about 50 mg artemisinine. *Artemisia annua* leaf tea has been used for thousands of years to treat malaria in China. [24, 25]. A portion of this reported increase in activity may be explained by the synergy of flavones found in the leaf, but not much more [26]. Considering the potential synergy that can arise from ingesting a plant extract or whole plant prompts the investigation of effects with shielding an active component from the metabolic activity of enzymes in the digestive system or in tissues or fluids that the active ingredient must pass through to enter the site of action. Another crucial prerequisite is the passage of membranes, which happen in the intestinal wall across the gut to the bloodstream and when a parasite, organelle, or host cell becomes infected. Transport may be aided by the presence of secondary compounds. Chemicals included in a plant extract may also regulate the function of messenger molecules, up- or down-regulate genes, obstruct phosphorylation or other protein activation, or induce other effects without being the active ingredient responsible for the therapeutic effect. Examples include preventing the ras protein from being prenylated or preventing ATP phosphorylation from activating the multidrug resistance protein. One may argue that plants present a variety of mechanisms for their own defence and that microorganisms that infect them will inevitably produce variants of themselves that are resilient to these defences. It follows that the presence of a wide range of compounds in plants that balance out the protective mechanisms conferring resistance to these compounds enhances the activity of the primary defensive principles.

Phenomena of Transportation

When the whole extract is ingested orally, the concentrations of components of plants in bodily fluids appear to be higher than when subjected to pure component. This observation suggests that the extract may have some protective effect, be actively transported across the intestinal wall, or inhibit or reverse excretory processes. Phospholipids are one class of plant compounds that have been demonstrated to provide larger plasma concentrations. For instance, when silybin, a hepato-protective flavano-lignan, is given orally to rats at a dose of 200 mg/kg, it is discovered in the plasma after an hour at levels that are either free or conjugated, approximately 0.005 µg/mL. However, when silybin is given via the same route as a complex with phosphatidylcholine, it is discovered in the free form at 8 µg/mL after 0.5 hours (plasma concentration against time plot: area under the curve - AUC 0-24h, 9µg/mL) and in the conjugated form at 74µg/mL after 1 hour (AUC 0-24h, 232µg/mL) [28,29]. Human patients showed similar patterns [30, 31, 32]. The complex's greater lipophilicity is thought to be the cause of the phenomena [33]. Phospholipids are present in plant tissues; however, the extraction procedure may cause some or all of them to be destroyed. Higher absorption levels and lower excretion levels might be anticipated if these lipophilicity-promoting substances are preserved in the extract, since NMR studies indicate a contact between the phenolic OH groups of flavonoids and the polar heads of phospholipid molecules. Furthermore, phospholipids comprise a significant portion of all cellular membranes that can dislocate from one side to another or be positioned to cross a membrane. Therefore, it is not unexpected that they can move related molecules across a membrane. The Milan group also demonstrated a significant improvement in the pharmacological effects of a standard *Ginkgo biloba* extract once it was mixed with phosphatidylcholine in further rat trials. Initially demonstrated for topical anti-inflammatory use [34], the rise in lipophilicity also had an impact on the oral bioavailability of Ginkgo flavonol glycosides as a cardioprotective drug, whereby they scavenge oxygen radicals to reduce postischaemic damage [35]. When soybean lecithin was added to baicalin, another flavonoid anti-oxidant found in the anti-allergic plant *Scutellaria baicalensis*, the plasma level increased in a manner akin to this [36]. Hydrogen bond connections can be formed between active molecules and other chemical groups, such as polysaccharides, which are frequently left out of phytomedicines during the extraction and concentration stages. They are commonly found in the aqueous and alcoholic extracts used in traditional phytotherapy, and a few studies indicate that they may

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be important adjuvants. For instance, Ohta et al. [37] reported on the apparent effect of fructo-oligosaccharides on bioavailability of isoflavone in mice, and Boik suggested that the use of mushroom polysaccharides in combinations for cancer chemotherapy is related to their interaction with other agents present. Proteolytic enzymes have long been recognised to facilitate the transit of big molecules across tight junctions, hence aiding in the transportation of medications across barriers [38]. But when it comes to naturally occurring medications, its usage appears to have been limited to allotherapy, as demonstrated by the simultaneous administration of tetracycline and bromelain [39]. In relation to the estrogenic and cardiovascular effects of soybean protein, which contains the estrogenic isoflavones genistein and daidzein, the topic of whether proteins may function as carriers of or can synergize small molecules has been raised. Though evidence say that soy protein-isoflavone combination is beneficial, recent articles do not address this subject [40, 41, 42].

Phase I and Phase II Enzyme Inhibition

A drug is affected by oxidation and reduction enzymes, many of which belongs the family of cytochrome P450 (CYP), and factors that attach hydrophilic groups on substrate to produce derivatives that are readily excreted by the kidney, including sulphates, glucuronates, or glycine amides, when it passes through the intestinal wall and the liver. The absorbed drug's plasma life is shortened by these two processes, which are referred to as Phase I and Phase II transformation or detoxification, respectively. Some secondary plant compounds have a common trait of inhibiting these processes; maintaining this property in a phytotherapeutic preparation may be essential to its effectiveness. Gilbert and Alves [27] tabulated some examples of experimentally determined inhibition of cytochromes, mainly as follows: curcumin from *Curcuma longa* and other *Curcuma spp*. (inhibits CYP1A1/1A2, 2B1/ 2B2), bergamottin 6´,7´-diol occurring, via the respective epoxy groups, from bergamottin occurring in grapefruit juice, which blocks CYP 3A4 (in the intestine wall), and resveratrol from grapes (blocks CYP 1A1). When grapefruit juice is consumed concurrently with synthetic drugs like the nifedipine group's antihypertensives, cyclosporine, an immunosuppressant, and others, the suppression of a cytochrome linked to the Phase I metabolism of the co-administered drug normally causes an increase in the drug's plasma concentration, perhaps to extremely high levels [43]. Nonetheless, Schulz [44], who cites papers that demonstrate discrepancies between clinical and research data, has pointed out that some experimental results need to be handled cautiously until supported by clinical observations. For instance, Obach [45] reports that extracts from *Hypericum perforatum* inhibit many factors of the CYP 450 group. However, clinical outcomes using cyclosporin have demonstrated that concurrent consumption of Hypericum by transplant patients can result in a high risk of transplant rejection because it lowers the immunosuppressant's plasma concentration [46, 47]. Stimulation of a P-glycoprotein drug carrier was assumed to be the cause of the lowering of digoxin, among other synthetic and natural medicines for which similar effects have been described, including indinavir, warfarin, and digoxin [48]. Therefore, clinical outcomes demonstrated that antagonism really occurred where the initial findings suggest that synergy must be found. Not unexpectedly, Markowitz et al. [51] demonstrated that Hypericum at recommended therapeutic dosages did not change CYP 2D6 or CYP 3A4 levels in healthy individuals. Furthermore, it is emphasized that, like the case of monoterpene hydrocarbons, a primary enzyme inhibition could be reversed and turn into a stimulation with repeated administration [49, 50]. Thus, in some situations, synergy may rely on usage frequency. The flavonoids, which have been known to impact cytochrome levels, have a synergistic effect with artemisinine derived from *Artemisia annua*. However, the mechanism behind this interaction is not demonstrated [25, 26]. It is currently impossible to anticipate whether this synergy would occur since a particular flavonoid may boost one CYP family enzyme while inhibiting another [51]. Phenolic and other hydroxy-compounds undergo glucuronidation and/or conversion to sulphates when they are absorbed into the bloodstream through the intestinal wall. When individuals consume soybean nutritional supplements containing daidzein, a soybean dihydroxyisoflavone, phase II metabolism converts the isoflavone completely into glucuronates (52 percent), sulphates (14 percent), and glucoronate-sulfates (34 percent) [52]. Hence, phase II transformation converts ingested materials into high polar molecules that are quickly eliminated. It was shown in vitro by Mésia-Vela et al. [53] that certain natural oxygen heterocyclic compounds inhibit the activity of a hydroxysteroid sulfotransferase (SULT 2A1) and of a phenolsulphotransferase (SULT 1A1).The inhibitors were xanthones (e.g., 11, IC50 for down regulation of sulfatation of dehydroepiandrosterone, DHEA, 8.5µM), coumarins, and rotenoids; these included elements of natural insecticides, such as rotenone (12, IC50 for DHEA, 11.3µM) and two coumarins from *Mammea americana* (e.g., 13, IC50 for DHEA, 15.7µM). The bioavailability of consumed pharmacologically active compounds that would otherwise be transformed to highly polar and easily eliminated conjugates is evident, even though this was not a synergy demonstration.

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Multi-Drug Resistance Inhibition

Multi-drug resistance is thought to arise from the abstraction of a foreign particle from a cell through the activity of a P-glycoprotein, Pgp, also referred to as MDR1-protein in mice. Pgp is a protein with 1278 amino acids that is found in the cell membrane and actually moves back and forth across it. The blood-brain barrier and the detoxification of cell cytosol in different tissues are both facilitated by this protein. Among its many functions, Pgp plays a role in intestinal absorption as well as biliary excretion since it is a transporter protein. The foreign molecule, which is usually lipophilic, is externalised by attaching to a lipophilic site on the MDR-protein chain by the of activation with ATP hydrolysis that takes place at certain ATP-binding sites. One strategy to stop the activation required for the process would be to block the ATP binding site. Another may be other tiny compounds that saturate lipophilic regions. Resistance develops, often a general resistance not particular to the treatment that triggered it, when drug molecules penetrate cells repeatedly, increasing the production of MDR protein and amplifying the related MDR gene [54]. The net effect is that a greater concentration of the active therapeutic ingredient is required to reach a desirable amount inside the cell. This is where using the whole extract rather than just an isolated principle might lower the amount of active ingredient required since the plant contains an MDR protein inhibitor. The majority of the several more examples found in the literature are of planar compounds, such as curcumin [56] and sanguinarine [55]. Large planar moiety is a feature of non-planar compounds, such as cinchonine or tropane alkaloid MDR inhibitors [58, 59]. Of all the groups, flavonoids are arguably the most significant. However, it appears that lipophilicity is required for high activity. This was illustrated by Perez-Victoria et al. [60], where the addition of a dimethylallyl group, as in 8-dimethylallylkaempferol, led to a significant increase in the flavonol's binding affinity with the C-terminal nucleotide binding domain of the MDR P-glycoprotein-type transporter of a daunomycin-resistant *Leishmania tropica* strain, in comparison to kaempferol itself. This was followed by a noticeable rise in the parasite cells' accumulation of daunomycin. A comparable flavono-lignan called silybin had similar results [61]. Adriamycin-resistant human myelogenous leukaemia cells significantly improved their absorption of vincrystine by quercetin, a flavonol linked to kaempferol, despite quercetin being inert [62]. Notably, highly methylated flavones are well represented in nature but were mentioned, for instance, in the synergy of artemisinine above. Dimethylallyl groups are very prevalent in natural aromatic O_2 heterocycles (note their incidence also in the most effective of the sulfotransferase inhibitors, 11–13, mentioned above). It has been demonstrated that flavonoids must be lipophilic, at least for their nuclear domain to bind to Pgp. In cases where polar flavonoids such as quercetin have been shown to enhance drug accumulation inside cells, it has been suggested that P-glycoprotein may not be associated [63]. The reported binding of green tea's epigallocatechin gallate to an MDR protein—possibly at a different site—seems to contradict this theory [57].

Additional Mechanisms

Certainty, the increases in active principle that are frequently observed when the original crude extract is kept are due to a variety of different molecular pathways. There are several examples of this, such as blocking isoprenylation, inhibiting protein kinases, and interfering with transport systems [27]. Because of the intricacy of plant extracts and also cell chemistry they affect, Schulz's [44] recommendation to wait to draw conclusions and see clinical results first will hold true for a very long time. It might be prudent to investigate if any of the components, which appear inert for the specific application indicated, could be enhancing the bioavailability of the active principles of many other plant components in the formula before dismissing old conventional formulations including many plants. For instance, as was already mentioned, curcumin functions as both an MDR and a Phase I inhibitor. Therefore, it is not unexpected that *Curcuma spp*., which contain it, are used so frequently in traditional remedies like Ayurveda. The idea that a plant employs its chemicals to fight its own enemies and that the pharmacological activity of these chemicals is improved in the natural formulas that are present may be the source of the widespread synergism seen in traditional phytomedicine. As in the case of *Artemisia annua*, fractionation and enrichment could damage the natural formulation and significantly increase the needed dose of the active chemical, which may result in an increase in toxicity as well.

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