Unlocking the Power of Therapeutic Synergy: A Comprehensive Review of Complementary Alliances Between Synthetic Drugs And Natural Compounds

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Abstract

Therapeutic synergy refers to the enhanced pharmacological effects that result from combining synthetic drugs with naturally occurring bioactive compounds found in nature. Recently, multidrug-resistant bacterial infections have become increasingly concerning, prompting efforts to eliminate these pathogens that pose a significant threat to human health. In treating other diseases, including cancer, diabetes, and cardiovascular issues, single synthetic drugs are becoming less effective each day. To address these various challenges in therapeutics, a synergistic drug system stands out as the most significant and conclusive formulation according to current pharmaceuticals. In modern pharmacotherapy, this combination heralds a new era. In contemporary medicine, the development of multi-targeted medications, which integrate synthetic compounds and bioactive natural substances, yields improved clinical outcomes with lower doses, fewer adverse effects, and reduced resistance. Therapeutic synergy is proposed to be more effective in treating cancer, neurodegenerative disorders, and infectious diseases. The pharmacokinetic interactions of the drugs facilitate easier absorption, metabolism, and bioavailability, enabling them to target receptors, enzymes, or ion channels more effectively, as well as modulating resistance pathways, including the inhibition of efflux pumps and disruption of biofilms. This is exemplified by the enhanced bioavailability of piperine and curcumin, as well as the flavonoid-mediated sensitisation of antibiotics. Furthermore, recent advances in omics technology, systems biology, and artificial intelligence have accelerated the identification and
mechanistic understanding of such interactions. Therefore, there is a massive opportunity to treat various deadly diseases effectively and sustainably by developing synergistic drugs in future pharmacology and pharmacokinetics. Thus, the present article aims to categorise, analyse, and provide expertise on combination drug therapy to develop medicines for future pharmacology, thereby improving human health and addressing disease conditions.

Keywords – Bioactive compounds, Drug development, Multidrug-resistant bacteria, Synthetic drugs, Therapeutic syne

Introduction

In contemporary medical research practice, there is a growing emphasis on integrating traditional medicinal knowledge with modern pharmaceutical advancements. One of the most promising areas of this convergence is the concept of therapeutic synergy. In this phenomenon, the combination of synthetic drugs and naturally

derived compounds produces a greater therapeutic effect rather than the agent alone. This synergistic interaction offers multiple clinical advantages,
including enhanced efficacy, reduced therapeutic dosages, and reduced risk of hostile effects [1].Chronic diseases such as diabetes, cardiovascular conditions, and cancer become increasingly prevalent worldwide; as antibiotic resistance poses a powerful challenge to global health, the pursuit of more effective treatment strategies has never been more acute [2] .

Therapeutic synergy has the power to address these challenges by optimising pharmacological responses while acknowledging and upholding the complex and multifaceted nature of many diseases [3]. Furthermore, this approach is consistent with the principles of personalised and integrative medicine, which aim to customise interventions to individual patient profiles and harness the entire range of therapeutic modalities—from advanced technological innovations to traditional, evidence-based natural remedies. Comprehending the mechanisms underlying these synergistic effects encompassing pharmacokinetic interactions as well as the modulation of molecular and cellular pathways—is crucial for the advancement of this field. A systematic investigation of these synergistic combinations has the potential not only to facilitate the development of novel drug formulations and combination therapies but also to help restore the therapeutic value of compounds that may be ineffective or toxic in isolation. Thus, therapeutic synergy constitutes a promising frontier in medicine, bridging the gap between traditional healing systems and modern biomedical science, promising more holistic and effective healthcare solutions.Therapeutic synergy indicates the combined action of two or more pharmacological agents produces an effect that exceeds the sum of their therapeutic outcomes. Its enhanced efficacy arises from several underlying mechanisms that can be broadly categorised into pharmacokinetic, pharmacodynamic, and resistance-modulating interactions. Firstly, Pharmacokinetic synergy includes interactions in which one compound enhances the absorption, distribution, metabolism, or excretion (ADME) profile of another; in this way, it increases its bioavailability and overall therapeutic potential [4]. For example, piperine—an alkaloid present in *Piper nigrum* (blackpepper)—has been observed to significantly increase the bioavailability of curcumin, as well as several pharmaceutical agents. At the same time, Pharmacodynamic synergy occurs when two or ore compounds have additive effects by targeting different molecular sites or physiological pathways [5]. This leads to a more powerful therapeutic response, sometimes allowing for lower dosages and reduced side effects. Finally, modulation of resistance mechanisms refers to another crucial dimension of therapeutic synergy, specifically relevant in the context of antimicrobial therapy.
This article focuses on understanding these synergistic mechanisms, which are drastically increasing in importance in modern pharmaceutical therapy. It specifically addresses the complexity of health challenges such as chronic diseases, multidrug resistance, and the requirement for more personalised treatment regimens.

Natural Compounds and Synthetic Drugs: A Compatible Alliance

Synthetic drugs are made through rational drug design and high-throughput screening and are characterised by their ability to precisely target particular molecular receptors, enzymes, and signalling pathways [6]. According to current estimates, about one-third of drugs in clinical use are based on natural products. This includes constituents either directly isolated from natural products, synthesised or semi-synthesised by structural modification of their natural compounds (Table. 1) [7]. Examples are colchicine, morphine, semi-synthetic aspirin, taxol and penicillin. The targeted mechanism of action ensures consistent pharmacokinetic and pharmacodynamics profiles,and it facilitates appropriate dosing and predictable therapeutic responses [8]. These limitations have prompted increased interest in adjunct therapies that can enhance efficacy while minimizing harm. Natural compounds, in contrast, are bioactive molecules derived from a wide range of biological sources, including medicinal plants, fungi, marine organisms, and microorganisms. These compounds sometimes exhibit structural diversity and pharmacological multiplicity, allowing them to interact with multiple molecular targets simultaneously. In spite of their
therapeutic potential, natural compounds faced a lot of hurdles to clinical adoption due to some issues, such as phytochemical variability, lack of standardisation, limited bioavailability, and insufficient evidence from large-scale randomised controlled trials [9].

Enhanced Efficacy: Natural compounds have the potential to increase the pharmacological activity of synthetic drugs by related pathways, improving cellular uptake and stabilising active drug forms. This results in improving clinical outcomes with faster or more encouraged therapeuticresponses.

1. **Decreasing Toxicity and Side Effects**: By increasing the therapeutic action of synthetic drugs day by

day,naturalcompounds may allow a depletion in the dosage of synthetic agents required [7]

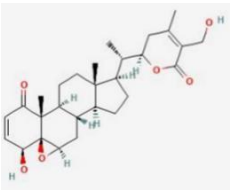
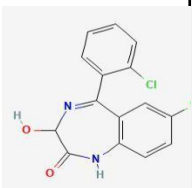
2. **Prevention of Drug Resistance**: There are a few certain natural compounds that have displayed the capacity to inhibit resistance mechanisms, such as efflux pumps, drug-metabolising enzymes, and mutation-driven target alterations [10]. This property isnspecifically favourable in the context of multidrug-resistant pathogens and chemo-resistant cancer cells, where traditional therapies alone often fail.

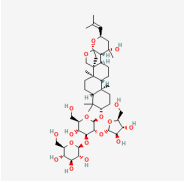
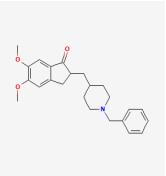
3. **Improvising Bioavailability and Metabolic Stability**: Some natural agents, such as piperine, have been observed to inhibit drug-metabolising enzymes (e.g., CYP450 andUGTs). The pharmacokinetic interaction may lead to more effective drug delivery andabsorption [11].

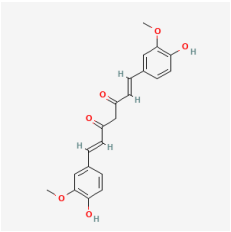
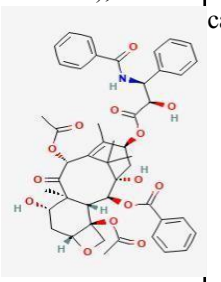
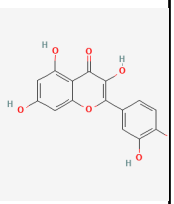
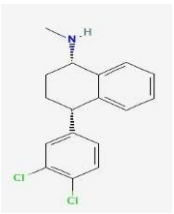
4. **Systemic Support**: Natural compounds often produce antioxidant, anti-inflammatory,immunomodulatory, and adaptive effects that contribute to overall physiological balance
[12]. These systemic benefits can accompany the narrow-spectrum action of synthetic

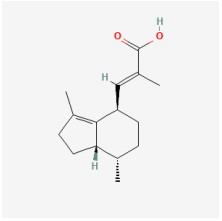
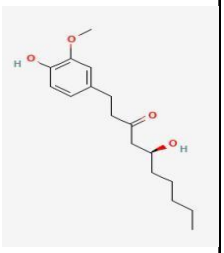
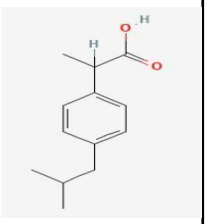
drugs. It can promote broader health outcomes and reduce treatment-related complications
In light of these advantages, the rational combination of synthetic and natural agents holds more sustainable therapeutic regimens.

Table. 1. Synergistic drug efficacy study against different diseases

SL. No	Name of herba product	Herbal product composition	Synthetic drug and its composition	Synergy mechanism	Uses in therapy	Reference
	Ashwagandha (*Withania somnifera)*	Ashwagandha contains a group of steroidal lactones called withanolides and withaferins. Alkaloids, such as isopelletierine, anaferine, cuseohygrine, and ana-hygrine saponins, which are natural detergents, contribute to its adaptogenic properties. 	Lorazepam. Its chemical structure includes a benzodiazepine ring system with a hydroxyl group and two chlorine atoms attached. Its chemical formula is C15H10Cl2N2O2. 	Ashwagandha synergise with lorazepam by: GABA modulation enhances GABA activity, leading to increased relaxation and reduced anxiety. Neuroprotective effects, where Ashwagandha's antioxidant and anti-inflammatory properties may help protect the brain from damage.	This Combination enhances anxiety relief and promotes relaxation. Help reduce stress and cortisol levels, and regulate sleep patterns.	[45]

	***Bacopa monnieri* (Brahmi)** is an Ayurvedic herb known for its cognitive-enhancing properties.	Contains ammarane-type triterpenoid saponins known as bacosides, with jujubogenin moieties as their aglycone units, and other compounds like hersaponin, herpestine, and  monnierin.	Donepezil It's a cholinesterase inhibitor which has an indanone core attached to the piperidine ring, which is connected via a methylene bridge.  Formula is C24H29NO3.	Donepezil inhibits acetylcholinesterase, but Brahmi supports acetylcholine levels, and enhance cholinergic signalling, and Bramhi decreases oxidative stress and neuroinflammation	This combined therapy use to improve memory, attention, and delay cognitive decline in dementia, Parkinson's, Alzheimer's disease	[46]

	Turmeric (*Curcuma longa*) Contains curcumin, a polyphenol.	Chemical composition includes diferuloylmethane (main active compound) and curcuminoids, consisting of curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcu  min (BDMC).	Paclitaxel is semi synthetic drug derived Taxus brevifoliaknown as taxol. It dissolve in Cremophor EL (a polyethoxylated castor oil), and  ethanol	Curcumin inhibit NF-κB, Akt a pathway promoting cell survival, proliferation. Curcumin enhance Paclitaxel's stabilisation of microtubules, inducing apoptosis in cancer cells	This combination used to treat various cancers, including breast, ovarian, and lung cancer and improve the outcome.	[47]
Ginkgo biloba also known as the maiden hair tree	Contains flavonoids (quercetin) and terpenoids, including ginkgolides and bilobalide. 	Sertraline is a serotonin reuptake inhibitor (SSRI). Formula is C17H17Cl2N and composed of 1-naphthalenamine, 1-(4-(3,4-dichlorophenyl) . 	Ginkgo biloba's flavonoids may increase cerebral blood flow, enhancing the antidepressant and cognitive effects of Sertraline.	Used in the treatment of depression with improved mood and emotional regulation.	[48]	*Ginkgo biloba* also known as the maidenhair tree

	Valeriana officinalis (Valerian root) have sedative effect.	Valerenic acid, valepotriates, isovaleric acid, and sesquiterpenes (modulator of GABA), flavonoids and alkaloids.  \	Diazepam is a benzodiazepine anxiolytic  composed of 1,4-benzodiazepine structure, formula C16H13ClN2O.	They acts upon GABA-A receptors by promoting sedation, muscle relaxant and anxiolytic effects.	This thera uses in insomnia, anxiety, or stress-relife.	[49]
	Ginger *(Zingiber officinale)* widely used in folk medicine.	Consiting Gingerols, Shogaols, Paradols, Volatile oils (zingiberene) 	Ibuprofen is nonsteroidal anti-inflammatory drug (NSAID) with the chemical name 2-(4-isobutylphenyl) propanoic acid.Formula  C13H18O2	Ginger's compounds Inhibit COX-2 enzyme reducing oxidative stress while Ibuprofen inhibits prostaglandin synthesis.	This synergisatio n enhanced anti-inflammato ry effects and pain relief	[50]

Case Studies in Synergy

The synergistic integration of natural compounds with standard synthetic pharmaceuticals has gained considerable attention in recent years, and it presents novel therapeutic strategies for the management of complex diseases. The following case studies show how such combinations can

enhance drug efficacy, overcome therapeutic resistance, and offer additional clinical benefits across diverse medical domains:

. **Cancer treatment**

The search for efficient combination therapies for cancer has focused completely on synergistic combinations as they exhibit therapeutic efficacy at very low doses. In cancer research, a growing body of evidence proves the adjuvant role of plant-derived polyphenols in enhancing the efficacy of standard chemotherapeutic regimens. Tumor cells are treated with synergistic, additive or antagonistic drug combinations such that the difference in therapy affects the proliferation probability or death rate [13]. Examples of a few Compounds such as *resveratrol* (a stilbene found in grapes), *epigallocatechin-3-gallate* (EGCG, principal catechin from green tea), and *curcumin* (a

polyphenolic compound derived from *Curcuma longa*) have Showed synergistic potential while mixed with cytotoxic agents like paclitaxel, doxorubicin, and cisplatin. These natural agents make the tumor cells weak by regulating key survival and apoptotic pathways, involving inhibition of NF-κB, PI3K/Akt, and STAT3 signalling [14]. Thus, they may downstream drug-resistance proteins (e.g., P-glycoprotein), thereby enhancing intracellular drug retention and cytotoxic efficacy. This type of synergistic interaction control promises to decrease drug dosages and dilute the dangerous effects associated with chemotherapy.

2. **Resistance of antibiotics**

Antimicrobial resistance (AMR) appears as a growing threat, with superbug pathogens such as *Enterococcus faceium*, *Staphylococcus aureus*, *Klebsiella pneumoniae* , *Enterobacter* sp. It has been observed that peptide k11 is a novel antibacterial agent and it resistant towards *Klebsiella pneumonia* [15]. It has prompted huge investigation into natural compounds like antibiotic adjuvants. *Berberine*, is an isoquinoline alkaloid which is isolated from species such as *Berberis vulgaris*, and exhibits potent display effects with various antibiotics. The primary mechanism includes the inhibition of bacterial efflux pumps, particularly the NorA transporter in *Staphylococcus aureus*, which enhances intracellular accumulation of antibiotics and restores bacterial susceptibility [16]. There are few essential oils, and their constituents—such as *eugenol*, *carvacrol*, and *thymol*—have been used to disrupt bacterial membranes, impair biofilm formation, and quorum sensing, thereby enhancing the efficacy of antibiotics against resistant strains.

3**. Neurodegenerative Diseases**

In the topic of neurodegenerative disorders, examples like Alzheimer's disease (AD) and Parkinson's disease (PD), natural compounds have displayed the potential to augment the effects of conventional pharmacological treatments. There are few compounds, such as biloba extract (EGb 761) and omega-3 polyunsaturated fatty acids (notably EPA and DHA) have demonstrated
neuroprotective effects when used adjunctively with standard therapies involving cholinesterase inhibitors and dopaminergic agents [17]. These compounds show their actions through multiple mechanisms, including attenuation of oxidative stress, reduction of neuroinflammation, and enhancement of synaptic plasticity. Preliminary clinical data suggest enhancement in rational performance and delay in disease progression, supporting the integrative therapeutic strategies in neurodegenerative care [18].
These case studies underline the importance of investigating synergistic interactions between natural products and synthetic drugs. This type of combination offer the potential of improve therapeutic outcomes and, enhance safety profiles and combat resistance mechanisms. As research in molecular pharmacology and systems biology advances, the integration of personalised and evidence-based medicine.

Mechanisms of synergistic drugs

Pharmacodynamic interaction - Pharmacodynamics (PD) is the study of the biochemical and physiological effects of pharmaceutical drugs. Pharmacodynamics places particular emphasis on dose-response relationships, that is, the relationships between drug concentration and effect. A simplified model of pharmacodynamic reaction is: L + R = LR. Here, L, R, and LR represent ligand(drug), receptor, and ligand-receptor complex concentrations, respectively. There are some principal protein targets with which drugs can interact: enzymes, Ion channels, and receptor interactions [19].

Receptor interaction – In this mechanism, a protein on the cell surface or within the cell binds to some specific molecules, such as drug molecules. The binding of it to a decoy activates or blocks the normal pathways. There are different types of
agonists that bind to the cell receptor to increase the cell's functions. First are competitive antagonists, which are types of molecules that bind to the cell receptor to block the agonist and decrease the cell's function. It can be overcome by
increasing the concentration of the agonist. Second, a non-competitive antagonist alters the receptor's conformation to block the agonist's function and decrease cellular activity, a process that cannot be overcome by increasing the agonist concentration. For example, GABA (gamma-aminobutyric acid), an inhibitory neurotransmitter that helps regulate neural activity, is affected by this mechanism. It receives at the target for various therapeutic agents like benzodiazepines, which bind with the GABA receptor and enhance sedative effects, such as sleep promotion.

A herbal compound, valerian, interacts with the GABA receptor and enhances the activity, promoting relaxation. The synergy between two compounds can enhance receptor activity and reduce the side effects of the synthetic drug [20].

B. **Enzyme interaction:** A drug binds to the enzyme, increasing or reducing its activity and thereby altering the metabolism of the substrate. When a drug binds to an enzyme, the interaction can affect its metabolism, concentration, and efficiency, also decreasing its toxicity. Example: Many antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are metabolised by CYP450 enzymes. St. John's Wort (*Hypericum perforatum*) is an herbal supplement that can induce CYP450 enzymes, particularly CYP3A4. This induction enhances its metabolism of it and can decrease its efficiency [21]

C. **Ion gated channel mediated pathway:** Ion channels are protein that regulates the flow of iron across the membrane and, influence cellular processes drug and modulate this by altering cellular signals. Ion channels are open or close in response
to membrane potential, are voltage-gated and depend on ligand binding are ligand- gated iron channels synthetic drugs that activate potassium channel can also ynergise with ginseng will enhance vasodilation and cardiovascular effects [22].

Drug Interactions

Drug Interactions can be of three kinds: **synergistic**, where a herbal medicine enhances the therapeutic effect of a synthetic drug, known as a synergistic effect. The synergistic effects of plant biomolecules and medications used as treatment options could be significantly effective [22]. Plant-derived compounds are often used to help minimise oxidative stress and cellular damage.

For example, resveratrol, a polyphenol derived from grapes and berries, increases the effectiveness of many chemotherapeutic agents. Following another mechanism of pharmacokinetic synergy, piperine, a bifunctional liver enzyme inhibitor of CYP3A4 and P-glycoprotein from black pepper, reduces a drug's metabolism, extending its working time [23].

Antagonism: Antagonism occurs when a herbal medicine reduces the effect of a synthetic drug or inducing toxicity. Antagonism is a result of adverse pharmacodynamic activity. Antagonism occurs via an enzymatic system, particularly the CYP enzyme system, which is vital in the systemic metabolism of drugs. An example is St. John's wort, a popular herbal antidepressant,
which induces CYP3A4 activity. Furthermore, Polyphenols in herbal teas can limit drug absorption by forming insoluble complexes with the active ingredients [24].

Additive Effects: Plant bioactive compounds and drugs work independently to enhance treatment benefits without altering their safety properties. There are many compounds like flavonoids, alkaloids and polyphenols that interact with pharmaceutical compounds. These plant-based molecules target different treatment pathways and also reduce the oxidative stress or inflammation caused by synthetic drugs [25]. This helps with healing properties and reduces drug side effects. For example, curcumin regulates cell pathways, reduces cellular

damage, and enhances the effectiveness of anticancer medications. Additionally, the flavonoid quercetin interacts with nonsteroidal anti-inflammatory drugs to reduce inflammation.

Pharmacokinetics interaction

It refers to the process where one drug affects the ADME pathway of another drug (A Adsorption, D = distribution, M = metabolism, E = excretion) (Fig. 1). These reactions can affect the synergy of herbal medicine and synthetic drugs. For example, the combination of sulfonamides and diuretics can cause alterations in drug plasma volumes due to metabolic changes resulting from an increase or decrease in the amount of drug antagonists present. Moreover, a synergistic effect can occur when the drug interacts with the gastrointestinal tract, the liver, and other body metabolism and excretion processes, such as the kidneys. Not only does this affect the pharmacokinetics of different drugs, but it also affects their absorption and regulates drug concentration and in vivo duration after use; it can also result in specific special effects, such as delaying the onset of corticosteroids [22, 26].

Adsorption: It's a process where drug travels through the blood circulation system and reached out to all body tissues and adsorpted by them.The pathway for the drug's journey can be from oral to intestine and liver and then it reached to bloodstream where it's bioavailability is decreased by some elimination process.To maintain the perfect amountof drug it can be delivered intravenously. Some factors like chemical properties of drug ,interaction with other substances, site of adminstration can effect the rate of Adsorption.Natural products, (flavonoids, alkaloids, and saponins) can modulate drug absorption in the gastrointestinal tract by modif it's solubility or influencing the membrane transport system. As example, tannins form insoluble complexes with drugs decrease adsorption and otherhand saponins altered cell membrane permeability increase adsorption. Furanocoumarin-rich grapefruit juice, can inhibit intestinal CYP3A4 enzymes, leading to the enhanced systemic absorption [27, 28].

2. **Distribution**: After the absorption the drug should be distributed throughout body to act upon receptor site. As first when a drug enterns blood circulation system it's bound to the most abundant plasma protein and became inactive throughout the rendering process . After achieving expected response the drug unbound and metabolise. The volume of distribution refers to a ratio of amount of drug present in tissue and blood . Blood flow , chemical characteristics affects this process . Plant biomolecule enhances the drug distribution by plasma protein binding and tissue permeability. Flavonoids are competitive binder to albumin, a main plasma drug transport protein, thereby changing the free drug concentration for its action . As example, plant substances can influence the blood–brain barrier's permeability by modulating efflux transporters (like p- glycoprotein), increasing
or decreasing the penetration of neuroactive pharmacologic agents [29].

3. **Metabolism**: The third process in pharmacokinetics is creating metabolites of drug by changing chemical alternation in many areas like the kidney, plasma, and gastrointestinal system in the body. The enzymes follow phase 1&2 metabolic pathways for the processing of drugs. In phase 1, the form of the drug in active metabolites, whereas phase 2 renders the compound inactive and water-soluble.CYP (Cytochrome P450) enzymes are responsible for most of the metabolism of drugs, and also it's elimination. Flavonoid warfarin can block cytochrome P450 enzymes by slowing the metabolism of drugs and promoting toxicity. As the opposite St. John's wort stimulates CYP3A4, leading to decreased blood levels during treatment with drugs. Plant compounds that are active in Phase II metabolisms conjugate with drugs like ibuprofen, bromelain, containing Phase II enzymes. Turmeric is a glucuronidation inhibitor that alters the metabolism of drugs [30].

4. **Excretion**: When a drug is not removed by the metabolism process, it is excreted vidifferent routes like liver, gastrointestinal tract, skin and most commonly through kidneys.A drug's PK is very much related to its renal function, as impaired function decreases the excretion of a drug. As a result, the accumulation of it can lead to toxicity. Renal blood flow, gastro PH, and age can affect drug excretion. The alteration of drug excretion via renal or biliary routes occurs in the presence of specific plant biomolecules when transporters and enzymatic modification in clearance processes predominantly contribute to an interaction. Some phenolics, such as methotrexate inhibit the transporters of organic anions in the kidney, leading to reduced excretion and increased risk of toxicity. Plantcomponents such as anthraquinones can change biliary excretion for drugs such as statins[28].

1. Herb drug interactions with body by pharmacokinetic mechanism ADME : Adsorption,Distribution, metabolism , excretion pathway

Practical Methodology for Analysing Herbal-Drug Synergy:

Identifying synergy combinations based on the protein-protein interaction (PPI) network:

Complex diseases involve multiple biological processes, making it challenging for single-target drugs to be effective. Thus, drug combinations can target multiple nodes in a biological network through synergistic effects. The PPIs are the primary interactomics system of any living organism. PPI networks can be used to predict potential synergistic drug combinations by analysing the

topology and centrality of the drugs. Various algorithms, such as NIMS, TSDS, and DrugComboRanker, have been developed to calculate synergy scores based on (PPI) network topology, gene ontology, and gene expression profiles. For the two-drug combination, evaluation scores, topology score (TS) and Agent score (AS) were created to evaluate drug synergy by an algorithm termed NIMS (network target-based identification of multicomponent synergy). The TS is the topology relationship among targets from different components. When a drug targets proteins which are close to each other on the PPI network, the TS for two drugs will be high. The AS is the phenotype similarity between the corresponding phenotypes of drugs [31]. Predictive

The synergy is based on TS and AS where AS is the phenotype similarity between two drugs. For Type 2 diabetes mellitus, Chandraprabha vati is a herbal medicine by chinese herbal medicine)has herb mineral ingredients help to exhibit glucose-lowering activity. This herb has a PPI network with glimepiride. This herbals ingredients 20-Hydroxypregn-4-en-3-one and Glimepiride build a network. Beta caryophyllene and Stigmasterol and also connect with glimpiride. This overall structure has the genes ESR-1,SRC ESR-1, EGFR,MAPK14, K3CA are located at the centre. This proves the PPI network and also the pharmacodynamics interaction between these two compounds[32].

Validation via quantitative models for detecting synergy: Isobologram Analysis:

The isobologram analysis is based on the Loewe Additivity Model, which assumes that the effect of two drugs in combination is additive, meaning that the impact of the combination is the sum of the effects of each drug alone. The isobologram plots the iso-effective doses of two drugs, which are

the doses that produce the same effect [33]. When two drugs don't show any interaction (synergism-or antagonism), the straight line represents additivity, showing that the effect of the combination is the sum of the impact of each drug alone: (D1 / ID1) + (D2 / ID2) = 1 [here, D1 and D2 are the doses of drugs 1 and 2 that produce a certain effect when given together. ID1 and ID2 are the doses of drugs 1 and 2 that produce the same effect when given alone.

For drugs to react synergistically, the isobole is concave upward, showing that lower doses of the combination produce the same effect. (D1 / ID1) + (D2 / ID2) < 1 Two antagonistic drugs results an upward convex line in isobole. It requires a higher dosage combination for achieving same effect : (D1 / ID1) + (D2 / ID2) > 1 [34]. In turmeric, a polyphenol curcumin exhibits anti-inflammatory and antioxidant properties. When it combined with AA (a synthetic pro-oxidant. It generates hydrogen peroxide-dependent cytotoxicity for cancer cells) showing synergy in an isobologram. This combination is more effective by enhancing activity.

An Isobolographic Analysis shows that a mixture of curcumin and NVP-BEZ 235 (a potent dual inhibitor of PI3K and mTOR) can synergistically induce apoptosis in human renal carcinoma Caki cells. It provoked cell shrinkage, chromatin damage in the nuclei and DNA fragmentation [25].

CI analysis: Synergy follows physicochemical mass-action law, which states that the ratio between the concentration of reactants and products is constant for a chemical reaction mixture that is in equilibrium. From this mathematical equation for the combination index (CI) was developed for the quantitative determination of synergy. When the CI value is < 1 (the more the CI value approaches 0, the stronger the synergistic effect),the synergy happens. When the CI value 1 it's additive and CI value >1 shows antagonism. CI based on the dose-response curves of individual components and their combination. CalcuSyn and CompuSyn softwares use to analyse. The mathematical equation is : CI = (D1 / IDx1) +(D2 / ID x2) [34]. Bioactive dichloromethane (DCM) subfraction of SCS and tamoxifen (antiestrogen drug) were studied using estrogen receptor-responsive and non-responsive breast cancer cells. Combination of SCS with low doses of tamoxifen produced 80% cell death, which proved to be a synergistic effect based on the method of CI using Calcusyn software. Polyphyllin I (PPI–active component from Rhizoma of Paris polyphyllin) and Evodiamine (EVO–active component from

Evodia rutaecarpa) were combined with Pt(platinum) or 5-Fu (5-Fluorouracil), which produced a significantly stronger inhibition rate on freshly-removed gastric cancer tissues from patients. The CI value <1 in and fraction affected (Fa) = 80% indicating a synergistic anti-cancer effect [25].

Optimisation of Dose by fixed ratio combination:

A combination therapy is not only working depending property of the drugs, but also depend on the dose ratio. Two drugs combined at a specific ratio considered as a third agent with its own dose effect relation. A multiple-ray design states a given set of fixed ratios (the one drug increased but other is constant) should be preferred .Once several fixed ratios are tested, the data can be analysed using CI analysis to identify the ratio showing maximum synergy. Also, 3D response surface analysis can effectively visualise and quantify the interaction across a broader dose range. As, the dose ratio should be optimised in preclinical studies before proceeding to clinical testing in humans.

Ex: Curcumin and 5-Fluorouracil (5-FU) used in Colorectal cancer have synergy at 2:1 or 1:4 ratio enhancing the apoptosis. Fixed ratio analysis and CI analysis method is used [35]. Berberine and Azithromycin combination used in MRSA treatment increases antibacterial activity at a 1:1 or 1:2 ratio synergistically. It's achieved by checkerboard assay and CI analysis [36]. Withaferin A combined synergistically with Doxorubicin at 1:1 or 2:1 ratio effective for breast cancer increasing
cytotoxicity, analysed by CI and Isobolographic method [37].

Challenges to face and reflection on synergy:

Therapeutic synergy between synthetic drugs and natural compounds holds a great impact on research and development but its practical implementation faced with several critical challenges that must be addressed systematically. To developing this synergy the fields are to be consider: standardisation, pharmacokinetic interactions, and clinical validation, all of which have significant implications for safety, efficacy, and regulatory approval.

1.**Quality Control and standardisation of product**

The integration of natural products into clinical pharmacotherapy could create a big obstacle due to the lack of consistent standardisation of those products. The chemical composition of natural compounds depends on a multitude of factors, including the geographical origin of the sourcematerial, harvesting conditions, methods of extraction, and post-harvest processing [38]. This variability can lead to fluctuations in bioactive compound concentrations, effecting pharmacological activity and efficiency of outcomes. To overcome this, robust quality contro protocols, which includes chromatographic fingerprinting, batch validation, and quantification of key phytoconstituents, should be used to ensure
consistency, safety, and regulatory compliance of product.

2.**Check potentiality for Drug-Herb Interactions**

Natural compounds, while generally termed as safe, but have pharmacological activity which interfere with conventional medications. A major concern is related with modulation of hepatic and intestinal cytochrome P450 enzymes (CYPs), which executes the metabolism of a vast majority of drugs [39]. Variety of phytochemicals, found in St. John's Wert, grapefruit, and ginseng, have been documented to induce or inhibit CYP enzymes, effecting the alteration of drug plasma levels by reducing efficacy or increasing toxicity. Other than this, natural products can affect drug transporters (e.g., P-glycoprotein), phase II conjugation enzymes (e.g., UGTs), and receptor sensitivity [40]. So, detailed pharmacokinetic studies and risk assessments are necessary before incorporating such combinations into therapeutic protocols.

3.**Lack of Robust Clinical Validation**

Though a significant number of studies report effective synergistic effects between natural and synthetic agents, the majority of these interactions deviated in animal models or in vitro experiments. Human clinical applications-based research remains limited. A well-designed, randomised, double-blind, placebo-controlled clinical trials is needed to confirm preclinical observations and its safety and by assessing long-term outcomes, and identify adverse interactions. Additionally, the response of drug varies in individuals due to genetic, environmental, and lifestyle factors which complicates the extrapolation of data in different population

underscoring the importance of personalised medicine therapy.

4.**Regulatory and Ethical Considerations for therapeutic synergy**

Natural product regulations differ across regions, with less stringent requirements than pharmaceuticals. This inconsistency prevents the integration of natural compound into formal treatment protocols, specifically where good clinical evidence and manufacturing standard. Ethical issues may include in clinical trials, particularly in vulnerable groups, when the safety of combination therapy is unclear [41]. Maintaining scientific integrity, standardised regulations and cross-disciplinary collaboration are essential to protect public safety.

In summary, a combination of synthetic and natural agents holds promise in modern medicine but requires modified scientific validation, strict quality control, and careful clinical implementation. To develop safe, effective, and evidence-based combination therapies, overcoming these challenges is necessary ..**Future Directions**

The future of therapeutic synergy relies on interdisciplinary convergence driven by technological advancements, regulatory innovation, and collaborative research. Integrating fields like pharmacology, systems biology, ethnobotany, medicinal chemistry, and clinical sciences is crucial to understanding complex interactions between synthetic and natural agents, ultimately yielding clinically effective therapies.

Use of omics technologies: These technologies, including genomics, transcriptomics, proteomics, and metabolomics which provide unprecedented insights into the molecular mechanisms and synergistic effects. These platforms are able to identify target pathways, biomarkers of response, and mechanisms of resistance at a systems level. Combining it with network pharmacology and systems biology modelling, multi-component interactions can be mapped which simulate biological responses and synergistic drug–natural compound pairs for further investigation [42].

Introducing artificial intelligence (AI) and machine learning (ML): These systems enable predictive modeling of synergistic interactions of drug herbs. These analyses vast datasets derived from experimental, clinical, and pharmacological sources to identify non-obvious combinations with high therapeutic potential. Silico screening methods can cut down the time and cost, enhancing the precision of hypothesis-driven research [43].

Proper clinical trial design: The evolution of combination therapies requires adaptive trial designs, real-world evidence, and personalised medicine approaches for dynamic and individualised responses. Involving patient-reported outcomes and biomarker-driven stratification can enhance therapeutic value. Regulatory frameworks should be modernised to balance innovation with safety. Regulatory bodies as the FDA, EMA, and WHO should consider

developing new pathways or guidelines addressing the distinct pharmacological and compositional quality of such combination therapies [44]. Public-private partnerships can accelerate discovery and validation, especially for under-researched areas like neglected diseases, orphan conditions, and many other infectious diseases.

In summary, the development of therapeutic synergy demands a forward-looking, interdisciplinary strategy that consists perfect regulatory innovation modern technology and promotes assist globa collaboration. By giving attention to these future directions, combination therapies deliver safer, more effective, and personalised treatments that integrate the best of modern science with traditional medicine.

Conclusion

To improve therapeutic efficacy, the combination of synthetic drugs and bioactive compounds is a very significant approach towards the development of modern medicine. This scientifically grounded approach is convincing in enhancing the efficacy of drugs against drug-resistant pathogens, as well as against numerous deadly human diseases. The synergistic drug approach is also convincing in minimising the dose of the drug and the development of resistance, furthermore by enhancing therapeutic efficacy. This multi-targeted drug-herb combination offers a new approach to treatment, leveraging the presence of naturally occurring bioactive compounds and synthetic drugs. Sophisticated remodelling tools, artificial intelligence, and an adaptive regulatory framework provide the support to develop therapeutic synergy for future medicine and medication.

Therefore, the evolution in medicine and pharmacotherapy will be more significant with the use of synergistic drugs for sustainable healthcare in future.

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