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Original Article

Anti-Inflammatory Effects of the Herbal Combination Sambiloto-Ginger-Turmeric (SIJAKUN)

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ABSTRACT

Herbal medicines are currently widely used, both in developing and developed countries. Herbal medicines with combinations of ingredients have complex chemical compositions, so identification of therapeutic effects is needed to support the use of these drugs in clinical decisions. The study aims to identify the therapeutic effects of the herbal medicine Sambiloto-Ginger-Turmeric (SIJAKUN) using *in silico*. A search for secondary metabolites in Sijakun was obtained from the KnapSack database, and then treatment predictions were carried out using WAY2DRUGPASS. After that, pharmacokinetic analysis was carried out using SwissADME. Protein targets that can interact with SIJAKUN using STITCH DB and SEA targets. Hypergeometric Test with Multiple Testing Correction Benjamini-Hochberg False Discovery Rate (FDR) was used as a statistical test. The combination of herbal medicine SIJAKUN has dominant properties as an anti-inflammatory and P53 stimulant via the JUN/AP-1 pathway. SIJAKUN meets the pharmacokinetic criteria to be used as a drug. However, it is less effective for absorption in the intestine. SIJAKUN can be used as an anti-inflammatory and anti-apoptosis drug, but laboratory tests and further research are needed regarding drug preparations to increase absorption in the intestine.

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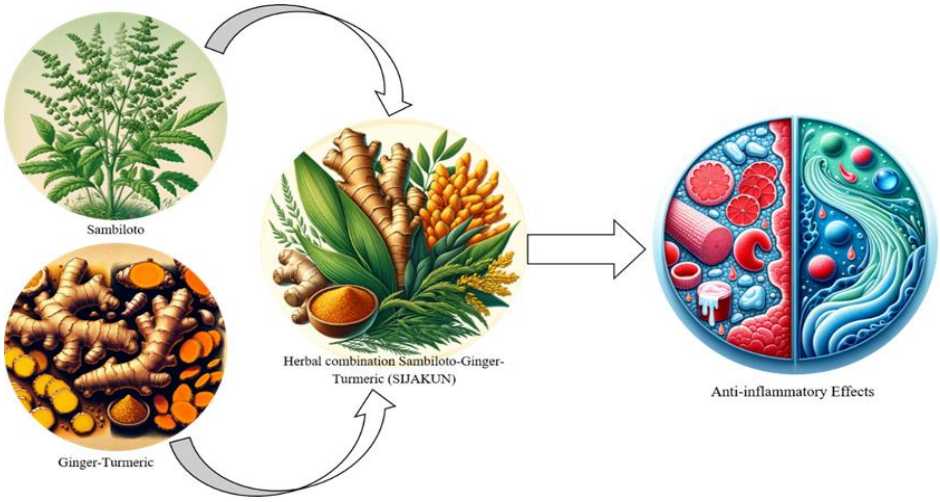
GRAPHICAL ABSTRACT



Introduction

Herbal medicines are currently widely used, both in developing and developed countries [1, 2]. Herbal medicines are believed to have health benefits without side effects [3-6]. In Germany, herbal medicine is quite popular, with a user prevalence rate reaching up to 19% in 2007 [7-10]. Curcumin, an important component of turmeric (Curcuma longa), which is a dimeric derivative of ferulic acid, has two o-methoxyphenol rings with a heptadienedione chain as a link [11]. Curcumin is a member of the Zingiberaceae family, which is widely cultivated in tropical regions of Asia and is widely used as a spice, flavouring, seasoning, and cosmetics [12, 13]. Apart from that, curcumin is also used as herbal treatment. Curcumin is believed to have anti-inflammatory effects. Antioxidant, anticoagulant. Anti-carcinogenic and anti-mutagenic through the activation of various cellular pathways [14-17]. Curcumin is able to inhibit proinflammatory transcription factors, including NFKB, activates the peroxisome proliferative activated receptor gamma (PPARy) cell signalling pathway and reduces the synthesis of proinflammatory cytokines related to NFkB, such as tumor necrosis factor-α, IL-6, and macrophage inflammatory protein 2 [18, 19]. Apart from turmeric, ginger and bitter are plants that are used as herbal medicine. In ginger, phenolic compounds consisting of shogaol and gingerol have anti-inflammatory, antioxidant, anti-cancer, and antimicrobial properties [20, 21]. Meanwhile, Sambiloto, which is known as "King Bitter", which is from the Acanthaceae family, has a therapeutic effect on its bioactive compounds including analgesic, anticancer, antidiabetic, anti-inflammatory, antimicrobial, antipyretic, antioxidant, cardioprotective, immunomodulatory, and neuroprotective [22]. Recently, the use of *in silico* human-based tools has been widely used in safety evaluations in the field of medicine [23, 24]. *In silico* can help in the identification of test molecules, prediction of results, side effects, mechanisms of action, and bioavailability of herbal medicines [7, 25]. In addition, the use of in silico can narrow the drug target so that it can reduce the time and costs of in vitro trials [26, 27].

In contrast to synthetic drugs, herbal medicines with a combination of ingredients have a complex chemical composition, so identification of therapeutic effects is needed as support in using these drugs in clinical decisions [28]. However, the therapeutic effect of the combination of herbal medicines bitter, ginger and turmeric (SIJAKUN) is still limited. Therefore, this study aims to identify the therapeutic effect of the herbal medicine SIJAKUN used in silico.

Materials and Method

Search for secondary metabolites

Sijakun secondary metabolite searches were carried out using the KnapSack and Dr. Duke databases. Each compound that has been determined is then searched for its canonical and isomeric SMILE (simplified molecular-input line-entry system) structure in the PubChem database.

Prediction of structure-activity relationship (SAR) of secondary metabolites as treatment

Secondary metabolites in search results were analysed for potential using WAY2DRUG PASS prediction. Previously, each compound needed to be searched for the SMILE structure obtained from the PubChem database. Then, the compound was analysed for its potential using WAY2DRUG PASS prediction. The Pa value (Probability To Be Active) is a value that describes the potential of a compound being tested. A Pa value of more than 0.7 indicates that the compound is predicted to have high potential [29].

Pharmacokinetic analysis of SIJAKUN

Analysis of the pharmacokinetic function of Sijakun in the body was carried out using SwissADME, and the relationship between absorption in the intestine and the brain was summarized using the Brain Or Intestinal Estimated permeation (BIOLED-Egg) model. The pharmacokinetic function of a compound is identified using Lipinski's rule of five. Compound toxicity and LD50 were predicted using ProTox and classification using the globally harmonized system of classification of labelling of chemicals (GHS).

Protein target prediction

Protein targets that can interact with SIJAKUN are predicted using STITCH DB V.5 and SEA Target (Similarity ensemble approach), with the minimum cut-off used being 0.57 [30].

Protein-protein interaction

Target protein interactions using STRING DB V.11 with an input high confidence score of 0.7 on the Homo sapiens organism. After that, analysis was carried out using Cytoscape version 3.8.2. to determine the role of proteins in the pathway. Plug-in GOlorize and Network Analysis in CytoScape were used in this research. The statistical test used is the Hypergeometric Test with Multiple Testing Correction Benjamini-Hochberg False Discovery Rate (FDR) correction with the ontology file Biological Process in Homo sapiens. Meanwhile, Network Analysis is used to determine the betweeness centrality (BC) value. BC is an analysis to see the role of the most dominant protein in the pathway being analysed.

Results and Discussion

Prediction of structure-activity relationship (SAR) of secondary metabolites as treatment

The analysis results show that the active compounds contained in the three plants are predicted to have antibacterial, antimicrobial, anti-inflammatory, anticancer, antiviral and antioxidant functions, with the highest PA values being anti-inflammatory and P53 stimulant (Figure 1).

SIJAKUN Pharmacokinetic prediction

The results of the pharmacokinetic function prediction show that the sijakun compound meets the criteria to be used as a drug (Table 1). However, the results of the BOILED-Egg analysis show that the active compounds from the Sambiloto plant are less effective in being absorbed by the digestive system (Figure 2).

Information : Molecule 1: [6]-Shogaol; Molecule 2: [8]-Shogaol; Molecule 3: [4]-Gingerol; Molecule 4: [4]-Shogaol; Molecule 5: 10-Shogaol; Molecule 6: Lutein; Molecule 7: Zingiberenol; Molecule 8: Quercetin; Molecule 9: 10-Gingerdiol; Molecule 10: [6]-Gingerdiol; Molecule 11: ar-Turmerone; Molecule 12: α-Turmerone; Molecule 13: β-Turmerone: Molecule 14: Curcumin; Molecule 15: Demethoxycurcumin; Molecule 16: Bisdemethoxycurcumin; Molecule 17: Dihydroferulic acid; Molecule 18: Ferulic acid; Molecule 19: Deoxyandrographolide; Molecule 20: Andrographolide; Molecule 21: Neoandrographolide; Molecule 22: Andrograpanin; Molecule 23: 7-O-

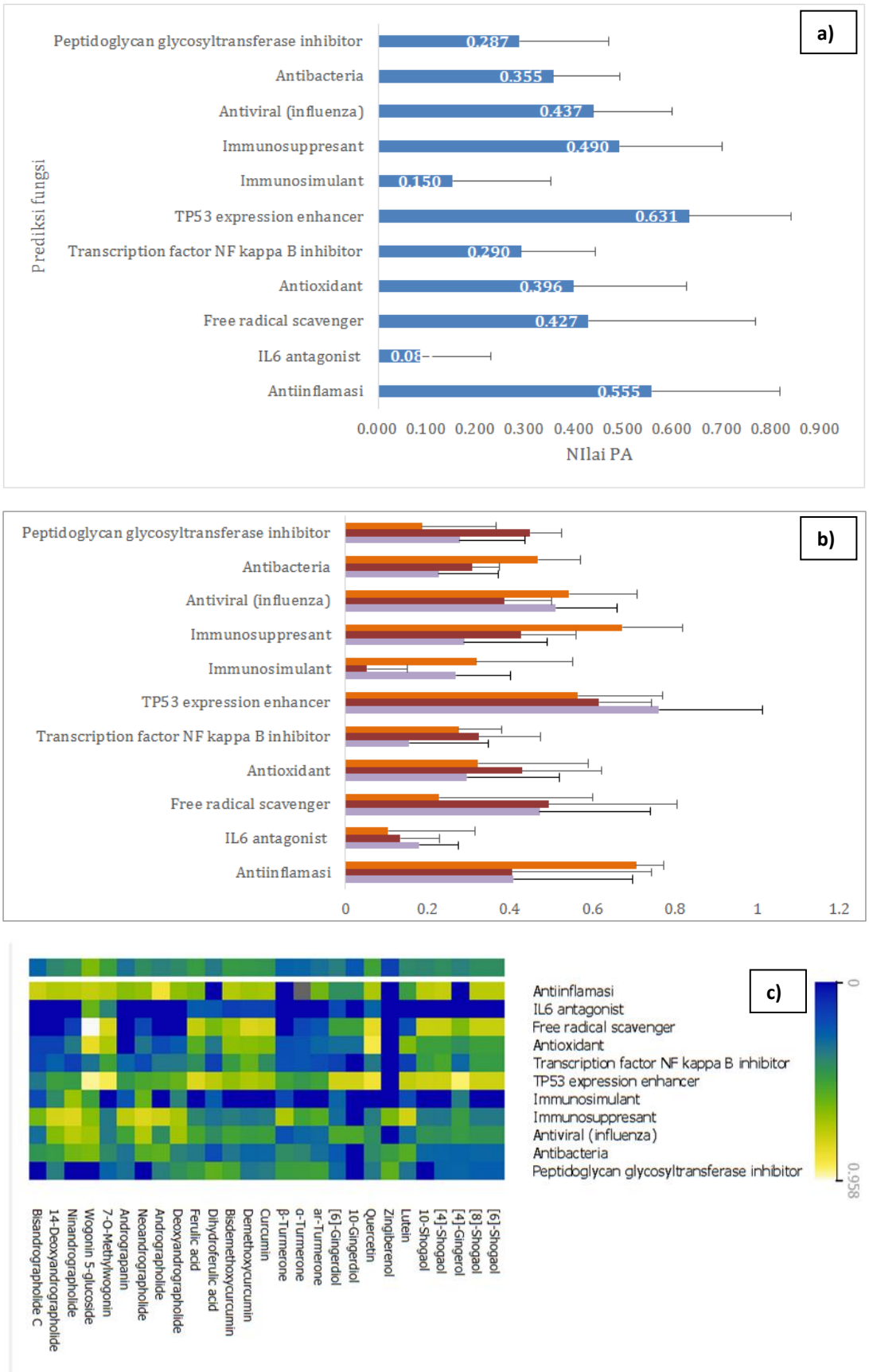


Figure 1: (a), (b), and (c) The results of the analysis predict the function of active compounds in Sijakun

Table 1: Average Lipinski rule analysis of 27 active compounds in SIJAKUN

Criteria	Result
Molecular mass less than 500 Daltons	326.95
High lipophilicity (expressed as LogP less than 5)	3.09
Less than 5 hydrogen bond donors	2.11
Less than 10 hydrogen bond acceptors	4.30
Molar refractivity should be between 40-130	95.31

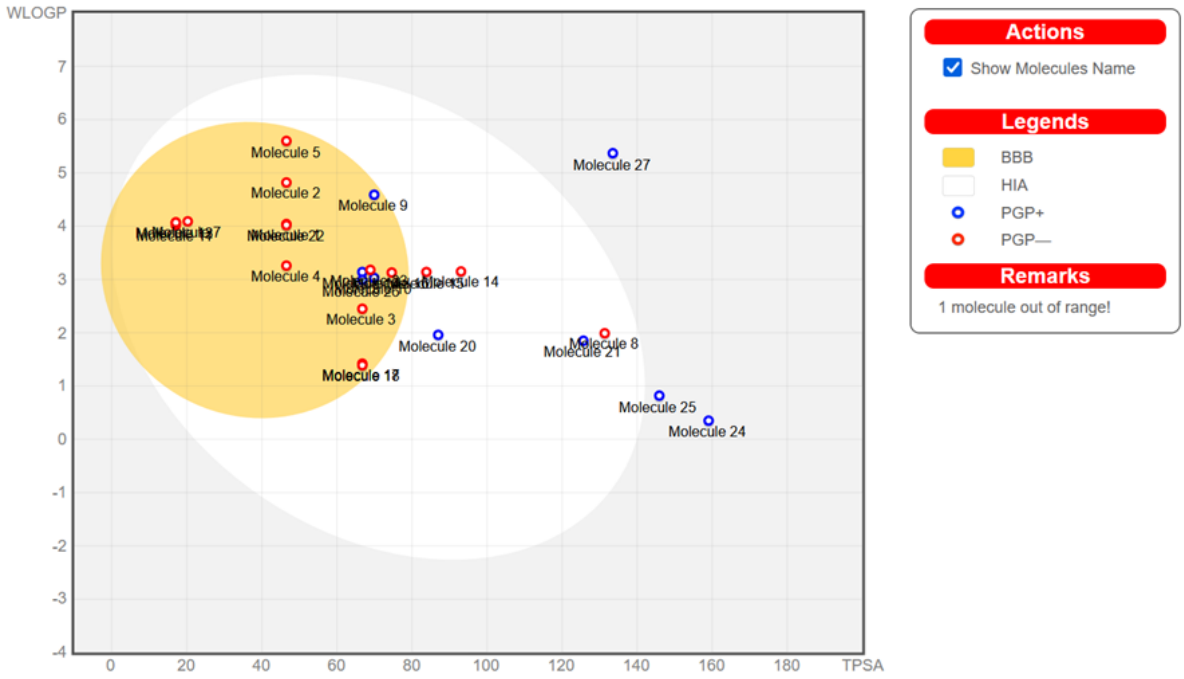


Figure 2: BOILED-Egg sijakun compound

Methylwogonin; Molecule 24: Wogonin 5-glucoside; Molecule 25: Ninandrographolide; Molecule 26: 14-Deoxyandrographolide; and Molecule 27: Bisandrographolide C.

In Figure 2, the white area is the physicochemical space of molecules with the highest probability of being absorbed by the digestive tract, and the yellow area (egg yolk) is the physicochemical space of molecules with the highest probability of being absorbed into the brain.

Target protein analysis

The compounds in SIJAKUN with the highest potential as anti-inflammatory were then predicted for their protein targets using SEA Target (Table 2). The SEA results used were those with a MaxTC value above 0.5, and proteins related to inflammation were selected. This selection of proteins is further illustrated in Figure 3. SIJAKUN Protein - Protein Interactions Related to Inflammation, which presents a detailed mapping of the interactions among these proteins. Because some compounds did not provide good results, additional analysis was carried out using STITCH DB (Figure 4) so that it could provide an overview of inflammation.

Table 3 indicates that the SIJAKUN Compound, the results of analysis using the PPI approach, shows that it targets many proteins/genes involved in apoptosis and stress responses.

Table 4 shows that JUN / AP-1 is the protein with the most dominant role in pathway analysis with a prediction score (0.368). IL4 is an additional protein that was deliberately added to help pathway analysis. Based on BC analysis, it shows that JUN / AP-1 is the protein with the most dominant role in pathway analysis, with a prediction score (0.368) (Table 4). Nuclear factor κB (NF-κB) and activator protein 1 (AP-1) (JUN) transcription factors play a role in regulating many biological and pathological physiological processes.

Table 2: Target protein prediction with SEA and STITCH DB

Ligand	Name	Description	Score Prediction	Source
Bisdemethoxycurcumin	FOS	Proto-oncogene c-Fos	0.6667	MaxTc From SEA Target
	JUN /AP-1	Transcription factor AP-1	0.6667	
	ESR2	Estrogen receptor beta	0.6538	
	MMP2	72 kDa type IV collagenase	0.6000	
	MMP9	Matrix metalloproteinase-9	0.6000	
	ESR1	Estrogen receptor	0.5152	
	CXCL12	Stromal cell-derived factor 1	0.5152	
	APP	Amyloid-beta precursor protein	0.5143	
	EP300	Histone acetyltransferase p300	0.5143	
	NFE2L2	Nuclear factor erythroid 2-related factor 2	0.5143	
	NFKB1	Nuclear factor NF-kappa-B p105 subunit	0.5143	
	TLR4	Toll-like receptor 4	0.5143	
6-Shogaol	ALOX5	Arachidonate 5-lipoxygenase	0.8372	
	CNR1	Cannabinoid receptor 1	0.580	
	CNR2	Cannabinoid receptor 2	0.580	
	CASP3	Caspase-3	0.700	Combinied Score from STITCH DB
	CASP9	Caspase-9	0.700	
Neoandrographolide	PTGS2	Prostaglandin-Endoperoxide Synthase 2	0.800	

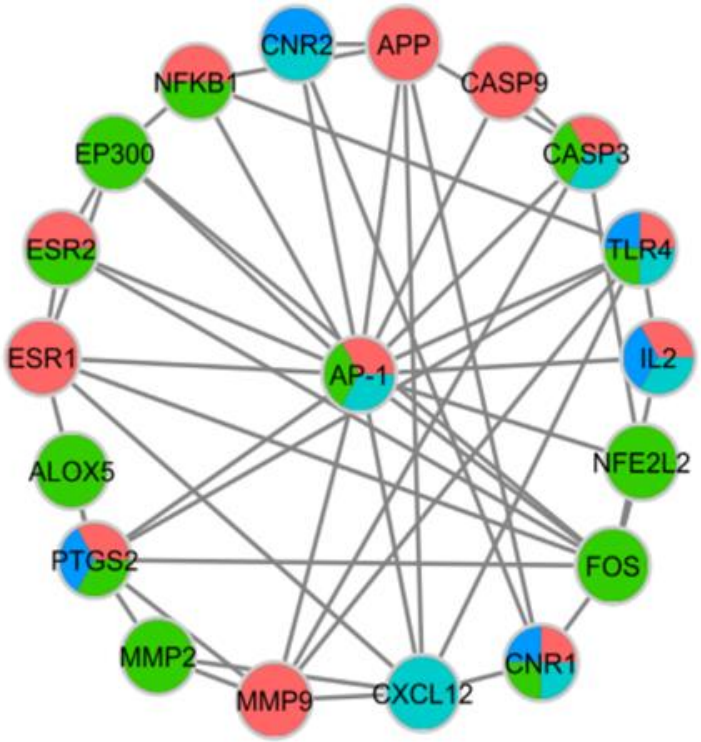


Figure 3: SIJAKUN protein -protein interactions related to inflammation

Table 3: Role of target genes/proteins in the pathway

Description	P-value	Corrected P-value	Gene	Gene total
Regulation of Apoptosis	0.00000000	0.00000002	APP AP-1 FOS PTGS2 ESR1 MMP9 IL2 ESR2 NFKB1 CXCL12 CNR1 CASP3 ALOX5 EP300 TLR4 NFE2L2	16
Respone to stress	0.00000028	0.00000940	JUN CNR1 MMP2 CASP3 ALOX5 EP300 FOS PTGS2 TLR4 ESR2 NFKB1 NFE2L2	12
Regulation of Inflammatory Respone	0.00000010	0.00000427	CNR2 CNR1 PTGS2 TLR4 IL2 ESR2 NFKB1 NFE2L2	8
Regulation of Immune System	0.00000071	0.00002132	JUN CXCL12 CNR2 CNR1 CASP3 TLR4 IL2	7

Table 4: Betweenness Centrality (BC) score of the analysed pathway proteins

Name	Betweenness Centrality
JUN / AP-1	0.315142
PTGS2	0.154902
FOS	0.107734
CXCL12	0.093573
APP	0.077342
MMP9	0.050545
TLR4	0.048203
ESR1	0.0439
CASP3	0.033769
CNR1	0.024237
NFKB1	0.010349
EP300	0.009804
MMP2	0.005447
NFE2L2	0.003268
IL2	0.002179

AP-1 is a member of the basic leucine zipper (bZIP) transcription factors consisting of the Fos (c-Fos, FosB, Fra1, and Fra2) and Jun (c-Jun, JunB, and JunD) families. C-Jun plays a role in cell growth and apoptosis [31, 32]. To prove this [33] used fibroblasts derived from c-Jun null embryos and showed that from this research, it was known that c-Jun was needed for development through the G1 phase of the cell cycle. Apart from that, c-Jun also mediates the G1 phase by playing a role in controlling the cyclin D1 gene. C-Jun collaborates with NF-κB to prevent apoptosis by inducing tumor necrosis factor-alpha (TNFα).

Activator protein 1 (AP-1) is a critical transcription factor that participates in many cellular processes, such as proliferation, apoptosis, differentiation, survival, cell migration, and transformation. AP-1 itself was proposed as a drug discovery target [34, 35].

The SIJAKUN compound analysed using the PPI approach showed that it targets many proteins/genes involved in apoptosis and stress responses (Table 3). Apoptosis is a programmed death process in normal cells. Apoptosis plays a very important role in the immune system because it plays a role in the immune response, antigen, and self-antigen recognition, as well as cytotoxic killing to maintain cellular homeostasis [36]. Meanwhile, stress is closely related to inflammation. Continuous stress can trigger chronic inflammation [37].

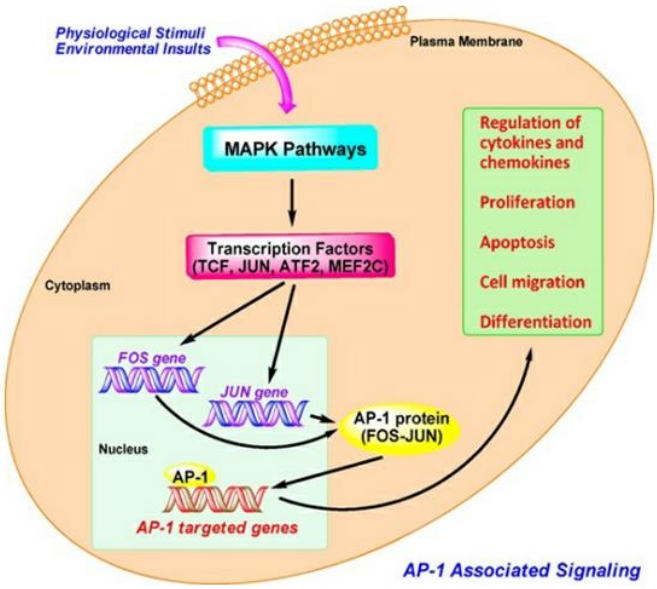


Figure 4: Small molecule inhibitors targeting activator protein 1 (AP-1) [34]

SIJAKUN compounds, which play a role in apoptosis and stress responses, can be used as therapeutic agents in several diseases, including rheumatoid arthritis, COVID-19, asthma, and SLE, which are associated with abnormalities in the immune system that trigger cell apoptosis, which can facilitate the occurrence of cytokine storms. Therapy using TNF antagonists (anti-apoptosis) in several studies has shown significant results in reducing severity [38-40].

Complexity of interactions among active Ccmpounds

The interaction among the 27 active compounds in SIJAKUN represents a complex network of biochemical dynamics. Each compound, with its unique molecular structure and pharmacological profile, can interact in various ways. These interactions can either enhance (synergistic) or inhibit (antagonistic) the overall therapeutic efficacy of the herbal combination. Understanding these interactions is crucial for optimizing the use of SIJAKUN in clinical settings.

Synergistic interactions for enhanced efficacy

Some compounds within SIJAKUN may work synergistically to potentiate the anti-inflammatory and P53 stimulant effects. This could be due to complementary mechanisms of action, where different compounds target varying pathways or receptors involved in the inflammatory process. For instance, one compound may suppress pro-inflammatory cytokines, while another enhances the body's natural anti-inflammatory responses, resulting in an amplified overall effect.

Potential antagonistic interactions

In contrast, antagonistic interactions may occur when one compound inhibits the activity or bioavailability of another. This could result from competitive binding to the same receptors or enzymes, or through metabolic interactions that alter the absorption, distribution, metabolism, and excretion of the compounds. Such interactions could potentially reduce the therapeutic effectiveness of SIJAKUN or lead to unforeseen side effects.

Clinical implications and safety profile

The interplay of these synergistic and antagonistic interactions significantly impacts the clinical efficacy and safety profile of SIJAKUN. Understanding these interactions helps in predicting therapeutic outcomes and potential adverse effects. This is vital for developing dosage guidelines, understanding contraindications, and enhancing the overall safety and effectiveness of the herbal combination.

Future research directions

To fully elucidate these interactions, comprehensive *in vitro* and *in vivo* studies are required. Advanced computational modelling and simulation can predict potential interactions, but empirical validation through laboratory and clinical studies is essential. Future research should focus on dissecting these interactions at the molecular level, contributing to the refinement of SIJAKUN formulation for optimal therapeutic benefits.

In exploring the therapeutic potential of SIJAKUN, a critical aspect is understanding the interactions among its 27 active compounds. These interactions, whether synergistic or antagonistic, significantly influence SIJAKUN's overall efficacy and safety profile. Synergistic interactions might enhance the anti-inflammatory and P53 stimulant effects, potentially offering a compounded therapeutic benefit. For instance, compounds that individually target different aspects of the inflammation pathway could work together to provide a more comprehensive anti-inflammatory response. Conversely, antagonistic interactions, where one compound inhibits or reduces the effect of another, could diminish therapeutic efficacy or alter the safety profile. Such interactions are particularly relevant in multi-compound formulations like SIJAKUN, where the combined effect of compounds can be unpredictable.

Understanding these interactions at a molecular level, possibly through advanced computational models or empirical studies, is paramount. This knowledge not only aids in predicting SIJAKUN's therapeutic outcomes, but also guides the optimization of dosage and formulation to maximize efficacy while minimizing potential risks. Therefore, a detailed investigation into these compound interactions is essential for realizing the full therapeutic potential of SIJAKUN and ensuring its safe clinical application.

Conclusion

SIJAKUN has potential as an anti-inflammatory and is predicted to target proteins that play a role in the mechanisms of apoptosis, stress, and suppressing the immune response/immunosuppressant. It is hoped that this in silicon-based study can be used as a reference in future research using laboratory animal tests and further research are needed regarding drug preparations to increase absorption in the intestine.

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