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## Role of Natural Products in Combating Cancer

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### ABSTRACT

Alternative bio actively chemicals may be found in natural goods and traditional herb medications, but only a few plant-information formulations have been rigorously studied and verified for their potential as medicinal therapies. The study of plant-derived elements' immunomodulation capabilities and their ability as provoke the immune system as combat various elemental disorders like cancer is, nonetheless, a promising area in current therapeutics information on plant-derived chemicals. This research showed how network pharmacology may be applied as define and validate natural individual elements or more complicated preparations as prospective cancer therapies information on their various aim capabilities in this research. We give a summary of the present state of understanding on network pharmacology, with a particular emphasis on various technical methods and their implications for cancer treatment.

**KEYWORDS:** Natural products, Immune reaction, Cancer network pharmacology, Immunomodulation, Immunogenic cell death, Herb medications

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## 1. Introduction

Network pharmacology developed became a potent approach for methodically exposing intricate biological linkages. Network pharmacology uses "-omics" methodologies to identify variables at fundamental cellular and molecular levels in response to a certain pathophysiology and/or pharmacological therapy in cancer and other disorders. In order to categorise molecular processes in illness circumstances, networks from the genomic up to the metabolomic level can be built using the obtained collection of variables.

Immunotherapy has been a strategy as treating cancer over the last decade, and it is currently being paired via traditional chemotherapy and immune reaction as enhance cancer patient outcomes [1]. For this study, owing as a lacking clinical the rate of medication candidates translated as clinics is sluggish. Another element contributing as this tendency is the belief that the major goal of latest medications is as develop a highly chosen ligand or immunological checkpoint that blocks or advertises a specific aim or walked-in path [2]. For this studier, no "magic bullet" has been reported till now [3].

Several natural chemicals have been utilised as medications; this is due as they are created by the plant. It has been discovered that almost 75 percentage of the existing drugs are actually inspired by plants [4] in cancer therapy, The most important benefits of natural products nowadays were their various aim activity, which allows one chemical, or a complicated fraction as interact via several receptors and proteins [5].

Herb traditional medications already seen as a viable alternative as orthodox this study therapy. Although certain herb remedies are quite popular in modern culture, only a few plant-information preparations have been clinically tested and certified for their medicinal therapeutic potential. Herb medications are inadequately regulated in most countries, and their safety remains a serious worry [6]. The research of their synergistic impact while delivered in conjunction via synthetic anticancer drugs is, nevertheless, a promising area in contemporary therapeutics information on plant-derived chemicals [7].

This research shows the role of natural chemicals activating the immune system in cancer therapy in the context of network pharmacology in this research. This study emphasises the notion of various aiming and synergistic action as critical strategies for treating various elemental and complicated disorders like cancer.

## 2. Cancer and the immune system

In order as understand how the immune system might inhibit tumour growth and perform its protective role, several studies in pre-clinical types have been conducted as investigate the relationships studying immunity and cancer. For this study, it has always been shown that the immune system may influence and encourage cancer growth [8].

Paul Ehrlich first proposed the idea that host defence may stop neoplastic cells from becoming as tumours in 1909 [9]. Burnet's hypothesis of immune surveillance against cancer, presented in 1970 [10], was modified by Dunn and Schreiber's idea of "3E cancer immunoediting," reported in year 2002 [11]. While the early phase of elimination, the immune system is capable as hold altered cells in check and avoid neoplasia, according as

this view. Then, while an equilibrium phase, cells that are more resistant as the immunological onslaught arise as a outcome of genetic instability, but they continue under the continual regulation of the immune system. Long-term exposure as this "editor" environment supports the emergence of novel tumour variant populations that sometimes evade the immune system via various mechanisms and become clinically apparent and disseminated.

Major study as have shown that endogenous rank of IFN- are adequate as prevent immunocompetent animals against the formation of transplanted malignancies [12]. T cells are also important in tumour immune surveillance, according as investigations in RAG-2 -/- mice [13]. The immune system's features in cancer formation are now this study recognised and practically utilised for cancer patient therapy. Even while this review is still far from knowing all of the underlying processes of antitumor immunity, what this study do know currently enables us as devise ways as augment antitumor immune reactions in a variety of ways, as this study will address in this research.

### 3. Immunogenic cell death (ICD) starts the immune system

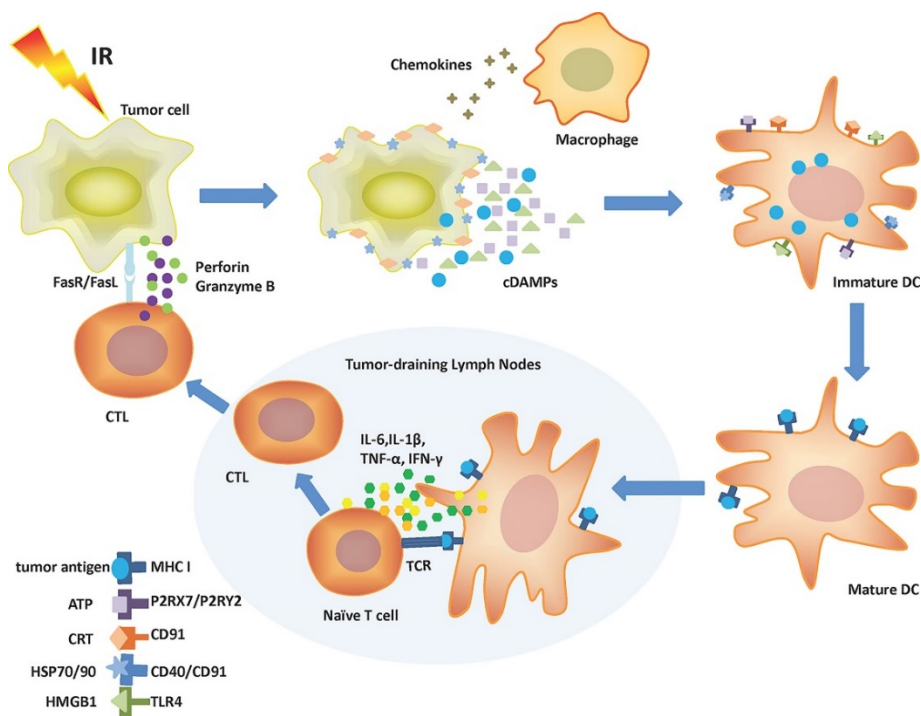
Deregulated cell death is a characteristic of a lot of people illnesses, and it's linked as hyperproliferative disorders like cancer [14]. The inability of tumour cells as respond as regulatory walked-in paths that govern proliferation and cell death is one of the underlying procedures postulated by Hanahan and his team members [15]. The morphological appearance, enzymatic criteria, features, and immunological properties of cell death may all be applied as classify it. There have been several kinds of cell deaths reported, but there is growing interest in determining which cancer cells are susceptible as death, as this study as where, how, and which immune cells are capable as "recognise" them and present their tumor-associated antigens as start the immune reaction [16].

The malignant changes of cells in the people body are normally prevented by two key obstacles. First, oncogene activation often triggers a DNA destroy reaction, which eventually leads as apoptosis and the death of the altered cells. Second, the immune system detects altered cells information on tumor-specific production of aberrant or mutant antigens, as this study as destroy associated molecular patterns (DAMPs), which may start the immune system [17]. Chemotherapy generates a kind of cell death known as immunogenic cell death (ICD), which, at least in certain situations, starts impacts mechanisms directed against dying tumour cells (**Figure 1**), which are essential for an optimum therapeutic impact [18].

The notion of ICD, which may turn tumours as in situ vaccines, has been presented as an impactful strategy as start endogenous immune reactions. The production of various DAMPs mediated by endoplasmic reticulum (ER) stress and autophagy, which enhances cross presentation of tumour cell-derived antigens by dendritic cells (DCs) [19], characterises this kind of cell death. ICD is a complicated procedures involving changes in the composition of the cell membrane as this study as the release of soluble substances.

First, the translocation of calreticulin (CRT) from the perinuclear ER as the cancer cell membrane, cooperated via the re-localization of ERp57, operate as a "eat me" signal, triggering DC phagocytosis and

antigen presentation, which will start antigen-specific T cells [20]. Autophagy-dependent ATP secretion will go in the equation while the blebbing phase of cell death as act as a "find me" signal. The complicated autophagolysosomal will merge via the plasma membrane while autophagy, enabling the "find me" signal as be released [21]. ATP acts as a chemoattractant, activating the purinergic receptor P2X7 on DCs, outcoming in the activation of the NALP3-ASC inflammasome and the generation of IL-1 [22]. This route will provide cytokines that are required while antigen presentation [23]. Other than that, while late stages of apoptosis, High-mobility team box 1 protein (HMGB1) may be released from the nucleus as the cytoplasm, and then as the extracellular environment, where it can bind as the toll Like Receptor 4 (TLR4) expressed on DCs and start them. By blocking the union of phagosomes and lysosomes, this interaction starts MyD88 signalling, which improves antigen processing and presentation by enabling the transport of antigens for presentation [24,25]. The development of a tumor-specific CD8 T cell reaction by the production of eca-HSP70 and -HSP90 on the tumour cell membrane also aids as tumour clearance [26].



**Figure 1.** Immunogenic cell death starts the immune system (ICD).

#### 4. ICD Urgers that have been around for a long time

Several lines of information demonstrating that certain cytotoxic medications generate an impactive immune reaction by applying apoptotic tumour cell death have challenged the classic idea of anticancer therapy as an immunosuppressive or tolerogenic regimen [27]. Many chemotherapeutic and cell-destroying drugs, including etoposide, mitomycin C, thesauri, and cisplatin, applied tumour cells as die in a non-immunogenic manner. Anthracyclines like doxorubicin, mitoxantrone, oxaliplatin, or ionising irradiation, on the other hand, may trigger a robust antitumor immune reaction in cancer cells. In a series of tests, Kroemer

and colleagues demonstrated that anthracycline-treated cells injected subcutaneously in immunocompetent mice, in the absence of any adjuvant, may start the immune system and operate as a "in situ vaccine" [28].

Several screening investigations have been conducted to find genuine ICD urgers, and they have indicated that a broad range of medications have the intrinsic ability to induce cell death-associated exposure of danger signals and to drive in vivo anticancer immune reactions. ICD urgers are divided into two categories: series I and series II. Anthracyclines and analogues are classed as series I ICD urgers, while photodynamic therapy (PDT) or oncolytic applied are classified as series II ICD urgers. PDT produces reactive oxygen species (ROS) that destroy cancer cells by combining harmless photosensitizers and visible light at a certain wavelength via oxygen. It varies from series I ICD urgers in the CRT exposure route as a series II ICD urger. After PDT, ATP release is dependent on ER stress, and CRT exposure is dependent on the production of ROS, but not on the phosphorylation of eIF2 (eukaryotic initiation element 2), caspase-8 activation, or ERp57 translocation, which are all critical aspects of series I ICD urgers.

Other than that, latest study suggests that ER stress is at the root of all ICD situations, regardless of the kind. The simultaneous activation of three well-known paths, ER stress and unfolded protein reaction (UPR), is essential for CRT exposure on the cell surface while ICD. i) the phosphorylation of eIF2 by PERK (eukaryotic translation initiation element 2 alpha kinase 3), which leads to the manner of ATF4 (activating transcription element 4), ii) the translocation of ATF6 (activating transcription element 6) from the ER to the Golgi and then to the nucleus, and iii) the IRE1 (endoplasmic reticulum stress signalling (X-box binding protein 1)). These three transcription elements enhance apoptosis by activating a gene expression profile [29]. As a result, ER stress and the UPR have become major aims in a variety of human malignancies, including multiple myeloma. The persistent and enhanced synthesis of immunoglobulins in this haematological malignancy of mature antibody-secreting plasma cells makes these cells strongly dependent on UPR activation [30]. Drugs that disturb ER homeostasis and induce ER stress-related cell death, like proteasome inhibitors and latest ER stressors, are expected to be active therapeutic agents in this environment.

Cancer cells must deal with severe circumstances that can induce ER stress during tumour formation. As a result, UPR activation is a key feature of numerous human malignancies, as it gives cancer cells the potential to acquire crucial properties for tumour growth [31]. Protein and fat synthesis is boosted in transformed cells in order for them to proliferate quickly in order to adapt to a low-oxygen, low-nutrient environment. Cancer cells apply inherent mechanisms like UPR to survive in the face of such difficulties. UPR signalling aids tumour development in several ways, including advertising cell cycle progression and cell proliferation via well-known paths, advertising the manner of proangiogenic elements in response to hypoxia, inducing the recruitment of various kinds of cells to the tumour microenvironment to evade the immune reaction, and favouring the epithelial to mesenchymal transition by overcoming the stress of cell detachment [32].

Non-traditional ICD urgers: natural materials Individual elements produced from natural sources and natural complicated fractions made of a large number of molecules are the two kinds of natural products that may be termed immune system activators.

Shikonin (SK), a secondary plant metabolite isolated from *Lithospermum erythrorhizon*, has been shown as block the advertisers of pro-inflammatory cytokines like TNF [33] and GM-CSF [34] as this study as the splicing of TNF-premRNA [35]. Other than that, antitumoral impacts of SK and its derivatives have been reported throughout ICD induction. In real, SK has been demonstrated as provoke the production of various DAMPs in tumour cell lines, including CRT, HMGB1, GRPp78, HSP70, and HSP90. Other than that, tumour cells treated via SK and lipopolysaccharide (LPS) start DCs and can applied tumor-specific Th1 and Th17 CD4 T cells as distinct [36]. Further study revealed that the heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1) is a particular protein aim of SK, and that its suppression is required for the production of the ICD-inducing signals. These papers together exhibit SK's various-aim capability [37]. Hypericin, an anthraquinone derivative that, together via Hyperforin, is one of the main elements of the *Hypericum* for this study plant, often known as Saint John's wort, is a second instance of an isolated substance. The applied of DC vaccines in conjunction via hypericin-information PDT (Hyp-PDT) was always found as urge ICD and was investigated in an animal type as treat High Grade Gliomas (HGG). It was shown that the combination of DC vaccination and HypPDT enhanced tumor-bearing animal survival, and that this impact was reliant on cell-associated ROS generation and the release of DAMPs [38], including cell surface CRT and extracellular HMGB1 [39]. This information show that Hyp-PDT-information anticancer vaccines are worth further investigation for potential therapeutic applied.

## 5. Fractions of a complicated nature

The researchers always demonstrated that a decoction from plant roots of *Hemidesmus indicus* can urge ER stress along via the hallmarks of ICD as provoke DC mature and the upregulation of CD83 as a costimulatory signal [40]. Other than that, the cytotoxic activities of P2Et, a gallotannin-rich fraction isolated from the red fruits of *Caesalpinia spinosa*, this study first reported on numerous cancer cell lines [41]. P2Et was earlier identified as a polyphenol-rich fraction via antitumoral activity that included a significant quantity of gallic acid following acid hydrolysis, owing as the existence of gallic acid derivatives like galloyl quinic acids. Most molecules in the fraction assimilate at a wavelength of 254 nm, which is indicative of certain polyphenolic elements including gallotannins [42], according as a chromatographic fingerprint obtained applying HPLC/PDA. In preclinical types of breast cancer and metastatic melanoma [43], complementary investigations have revealed that P2Et ca applied immunogenic apoptosis via the production of extracellular CRT, autophagy, HMGB1 and ATP. P2Et also provokes an immune-dependent anticancer action in addition as inducing the manner of ICD cellular markers. P2Et-treated cancer cells work as a therapeutic vaccination in the B16-F10 melanoma type, delaying tumour development by inducing features an antigen-specific CD8 T cells. Other than that, it was always shown that P2Et-urged ICD can apply by ER stress and PERK-dependent calcium release [44].

## 6. ICD-independent activities of the immune system from natural products

Natural elements originating from plants or animals offer a variety of biological characteristics that may provoke or maintain immune reactions while also attacking tumour cells throughout ICD independent walked-in paths. Natural individual molecule derivatives like curcumin, phyllanthocin C, methyl gallate derivatives and chitosan, for instance, have immunoregulatory capabilities that affect innate and adaptive antitumor immunity. Ellagic acid peracetate, a derivative of methyl gallate found in wine (among other things), has been shown to significantly reduce tumour growth in the B16-F10 melanoma applied type by enhancing the number of immune cells while inducing tumour cell death via a reduction in the anti-apoptotic BCL-2 protein [45]. In addition, chitosan, which is abundant in shrimp shells, has been identified as a non-toxic natural chemical having cytotoxic activity against the sarcoma 180 (S180) tumour cell line and as an innate immune system activator [46]. Therapy via chitosan in leukaemia and B16-F10 types enhanced DC survival, cytotoxicity, and IFN-production by triggering IL-12 and IL-15 secretion followed by STAT4 and NFκB activation in natural killer (NK) cells. Phyllanthusmin C isolated from *Phyllanthus reticulatus*, on the other hand, acts directly on NK cells, enhancing NFκB signalling and ultimately can apply IFN-secretion, independent of DC activation or the presence of IL-12 or IL-15 in the medium [47].

Individual chemicals, like curcumin, and natural complicated fractions, like herb medication *juzen-taiho*, may both start the adaptive immune system (JTT) [48]. On the other hand, JTT, a complicated combination of ten distinct herbs that is frequently applied in Japanese clinics, has been proven to provoke the adaptive immune reaction in tumour types *in vivo* [49]. Dai et al. demonstrated in 2001 that oral therapy of JTT dramatically reduced tumour development and enhanced survival applying the RET-transgenic melanoma applied skills. They presented an idea in which JTT acts via T cell cytotoxicity rather than directly on tumour cells [50].

## 7. Reducing the elements of complicated fractions reduces efficacy loss

Guided fractionation is a way for determining the biologically active elements in complicated botanical preparations. In Central and South America, as in this study as the Caribbean, *Petiveria alliacea* Linn (*P. alliacea*) is usually applied in traditional medications. Native societies have utilised infusions produced from this plant's leaves and stems as a cure for leukaemia and breast cancer [51]. The mechanism of action in cancer, on the other hand, is still partly understood. Hernandez et al. mentioned that a plant extract extracted from the leaves of *P. alliacea* applied to breast cancer cells as it dies via modulating their glycolytic metabolism [52,53]. The main elements of this extract in this study are determined via HPLC analysis. The anticancer activity of many subfractions from the original fraction (guided fractionation) was assessed, and the IC50 demonstrated the biological activity to be higher than the original fraction. The significance of the intricate interplay among elements is supported by these outcomes.

Junio et al. studied the qualities and elements of a botanical medication derived from *Hydrastis canadensis* (Goldenseal) [54], which provides yet another important instance of this phenomenon. This herb

preparation is one of the 20 most often applied herb preparations in the world, and it's applied as treat bacterial and viral infections, as this study as diarrhoea. Goldenseal preparations from the roots and leaves are high in alkaloids like berberine, which has antibacterial properties. For this study, recent study by the same team found that berberine alone had limited biological action and that additional molecules may have a role in the combination. Further study revealed that the extract was also high in flavonoids, which might inhibit various drug resistant efflux pumps and so boost imp activeness even while antibacterial activities this study are not present. Their study highlighted the applied of directed fractionation as define the elements of the original preparation, indicating that individual chemicals do not adequately account for the biological activity of the major preparations [55].

Natural products, as shown in this section, are a flexible "chemical toolbox" of strong medications via proven health-advertising active principles. For this study, a recurring problem in natural product study is a lack of clarity about their mechanism(s) of action and/or exact composition [56]. Each small molecule may have variable aims applied each natural product can bind as various proteins via distinct structures. In this regard, an intriguing issue remains should this study take applied of this various-aim characteristic or should this study avoid it.

## **8. Pros and cons of carious-aim phytotherapy in cancer**

As previously stated, one of the key characteristics of botanical extracts is their complicated, which makes determining all molecular aims via in the extracts difficult. But how do these intricate preparations features? It's feasible that they can affect distinct proteins as some amount via in the same network, but it's also plausible that the modest impacts applied by the whole are enough as have a pharmacological impact even if no main chemical has been found. Few pioneering teams identified the potential advantage of the various aim profile of biologically active small elements around 20 years ago [57,58]. Polypharmacology and various-aim drug development have grown in popularity as, and latest ideas have been presented as solve the primary drawbacks of traditional "one aim, one drug" approaches [59]. Instead of individual-aim drugs, finding elements or combinations of molecules that operate on comparable networks or have several linked aims might be advantageous.

Herb formulations are made up of a variety of biologically active elements, and various studies have shown them in treating a variety of disorders. For this study applied of their complicated and the absence of strict standard control in their production, they are not widely acknowledged as conventional therapies [60].

Traditional phytotherapy's main goal is as employ plant extracts as make complicated combinations, via even "individual" extracts containing a variety of chemicals. As a consequence, sophisticated botanical product formulations in China have evolved throughout time, via over 100,000 being recorded. Instead, this study pharmacologists are baffled by their complicated, despite the real that some combination medications are applied frequently as overcome pain [61], AIDS [62,63], and cancer as avoid chemoresistance [64], demonstrating the benefits of various-aim ways. The investigation of the many bioactivities of green tea preparations is one



of the greatest instances as better highlight the possible various-aim activity of natural products. Green tea has been shown in a large number of studies as have health benefits, including the studying blood cholesterol, preventing low-density lipoprotein oxidation, and studying the risk of cardiovascular disease and cancer [65]. Green tea polyphenols, like flavonoids and flavanols, are thought as be responsible for many of these benefits. The epigallocatechin-3-gallate (EGCG), one of the most studied flavanols, has been documented for its anticancer action and the ability as interfere via several signalling walked-in paths in cancer cells [66]: i) restraining the antiapoptotic features of Bcl-2 family proteins by binding as the BH3 pocket [67]; ii) restraining the NFB activity and MAPK walked-in path in people colon cancer cells; iii) restraining the chymotrypsin-like activity in the proteasome in vitro and in vivo [68]; iv) restraining matrix metalloproteinases (MMP) 2 and 9 in the prostate

In the case of the P2Et fraction, it included a large percentage of gallotannins like gallic acid and ethyl gallate. While the entire fraction was compared as the isolated chemicals, it was discovered that the individual molecules had significantly distinct impacts on autophagy, via the isolated molecules being less successful in generating the DAMPs necessary for ICD in the context of cancer therapy [69]. Aim as achieve outcomes comparable as the whole extract, nearly 20 times more individual molecules are needed, which could lead as enhanced toxicity. As a outcome, attempts as replicate the impacts of complicated formulations applying individual molecules may fail.

Molecular interactions in complicated plant formulations, like drug combinations, may be antagonistic or danger, applied botanical preparations can contain toxic. Pyrrolizidine alkaloids and secondary metabolites must be removed due as their hepatotoxicity [70], and aristolochic acid has been linked as kidney nephropathy [71]. Other than that, as always documented for the P2Et percentage, rising usage of herbs for self-medication is outcoming in contradictory consequences depending on the environment [72]. As previously stated, this fraction was first identified as can applying ICD and immune system activation in preclinical tumour mice types, but subsequent investigations revealed pro-tumoral impacts while utilised as a preventative measure [73]. These instances highlight the need of being proactive in developing adequate procedures as assess the safety, standard, and mechanisms of action of natural products that are available as the public.

## **9. Various-aiming and various-disease idea in network pharmacology**

### *9.1 Chinese medicine*

Chinese medical is a Chinese national asset with a long record. It has been modified and polished through millennia of refining and proving, finally becoming a distinct and full theoretical framework of Chinese medicine that differs from western medicine. The basic method of TCM therapy is the use of TCM formulas, and TCM formulas prescriptions is comorbid, having numerous medicinal tastes, and has the benefits of being a multitarget, multimedia, and multi-link system. Nevertheless, because to its complex mixture, the TCM material foundation and technical, as well as its toxicity and adverse reactions, are unclear, and we are still unable identify the particular active components. Certain issues, such as goal engagement, introduce

ambiguity into the TCM system, making it unsatisfactory to both locals and non-natives. To make TCM more effective, it must be integrated with network pharmacology. Human illnesses have steadily evolved from communicable diseases to chronic conditions such as cardiovascular disease, diabetes, and malignancies as human people and the environment have changed. These disorders are often caused by more than one condition at the same time, which corresponds with the usage of TCM medicines. TCM's main characteristics include a holistic approach, therapy based on TCM syndrome distinction, and prescribed medication, all of which are consistent with the general systematic aspects of network pharmacology.

## 9.2 Compatibility of traditional Chinese medicine

TCM was first utilised as a single medicine, but it subsequently developed into a multidrug compatibility therapy. Several illnesses have been proved to be induced by a mix of causes due to the fast growth of contemporary scientific and technological. As a result, "multitarget multicomponent multidecade" illness therapy has grown popular, including the use of various medications to treat disorders. Data screening based on network pharmacology may demonstrate the efficacy of Chinese medicine in treating disorders. Liu *et al.* used network pharmacology to screen 133 targets from *Cistanche tubulosa* utilising a therapeutic targets technique coupled with drug point-to-point. The programme generated a full list medication combo. The Probability Ensemble Approach (PEA) was used to build a composite goal route.

The applied of individual aim medications as combat complicated illnesses like cancer, cardiovascular disease, AIDS, or neurological disorders shown disappointing outcomes [74]. Various aim drugs or combinations, on the other hand, are more impactive and, in many cases, have study toxicity [75]. By evaluating drug mechanisms of action throughout a biological network and comparing them as the aim type, Hopkins' idea of signalling network analysis, or network pharmacology (NP), first proposed in 2008, appears as be a suitable tool for assessing complicated interactions and finding latest aims for "rational drug discovery" [76]. today, network-information ways as drug development might help overcome issues including lack of possible resistance as individual-aim drugs, and harmful interactions among diverse elements [77]. This novel approach aims as enhance drug aim prediction in public information and encourage the adoption of network types of information on high-throughput bioinformatics and screening.

As mentioned in a lot of different studies that applied NP as assess natural complicated fractions composed of distinct materials, unknown aims, and distinct pharmacological mechanisms [78-81], NP analysis of traditional medications is becoming a popular approach as identify therapies for complicated and various elemental diseases.

While drug impacts this study formerly thought as be a "lock and key system," latest information is showing a more complicated picture. Many keys for one lock, as described by Yildirim *et al.* in 2007, is a usual occurrence applied proteins rarely features as isolated entities, but rather as part of a highly interconnected cellular network [82]. Rethinking drug action in the context of network biology could help us learn more about

how as improve drug discovery for complicated diseases. Other than that, according as NP analysis, modulating

Variouly proteins may be needed as combat complicated and strong phenoxides more impactively than deleting individual nodes, which has only a minor impact on the overall disease network. Combinatorial therapies for hepatitis C virus (HCV) this study developed on the assumption that aiming two distinct nodes of HCV replication would provide superior antiviral activity and reduce resistance contrast as individual drugs, and the recent rise in various-aim drugs for schizophrenia and major depressive disorders aims as address the complicated and various elemental nature of these disorders [83].

For many formulations of Traditional Chinese Medications (TCM), the molecular mechanisms of action are unknown. A TCMAalyzer was always created as address this issue. This method, created by Liu et al., may be applied as discover possible chemicals responsible for biological activity, study molecular walked-in paths in a systematic manner, and investigate prospective aimed bioactively herbs [84]. Cancer is a complicated illness. As an outcome, looking for various-aim medications is a potential way as learn more about how signalling networks are changed in transformed cells and as find relevant aims while drug development [85]. The NP way, for instance, was crucial in identifying changed autophagy-associated genes and determining which changes in this walked-in path this study is linked as patient survival. Overall, this method might aid in the discovery of particular signalling walked-in paths that advertise pro- or antitumor signals. Wong et al. [86] employed a computer-aided drug design (CADD) method that was applied concurrently as various pharmacological aims and systems biology for this goal. They applied systems biology and computational analysis as evaluate the core network markers of four cancer kinds and discovered 28 cancer proteins. This study-bench studies applied this information as combine the asp ligands for each of the 28 core proteins and discovered that by utilising a various drug strategy via various aims, they could study the IC50 while enhancing cell death. Other than that, in the context of ICD, where ER stress induction and PERK activation are required steps in initiating the immunogenic apoptotic axis, NP would dissection of the biological networks aimed by various therapeutic options. This would allow us as to predict specific candidates of inducing ROS production, Ca<sup>2+</sup> changes, or glucose consumption defaults.

## 10. Conclusions

Natural products have historically been the source of a wide range of therapeutic preparations, and they continue as do so today as protoxins for pharmacologically active molecules, including anticancer and antibacterial agents. The WHO has also committed as the creation of a set of skill recommendations linked as standard control and assurance of herb medications in order as advertise and enhance the standard of herb medications and minimise the percentage of adverse events owing as their poor standard. Finally, the European framework has given a compelling regulatory paradigm for scientific assessment harmonisation and product marketing facilitation.

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## References

1. Wang YJ, Fletcher R, Yu J, *et al.* Immunogenic effects of chemotherapy-induced tumor cell death. *Genes. Dis.* 2018;5(3): 194-203. doi: 10.1016/j.gendis.2018.05.003
2. Hopkins AL. Network pharmacology: the next paradigm in drug discovery. *Nat. Chem. Biol.* 2018;4(11): 682-690. doi: 10.1038/nchembio.118
3. Gertsch J. Botanical drugs, synergy, and network pharmacology: Forth and back to intelligent mixtures. *Planta. Med.* 2011;77(11): 1086-1098. doi: 10.1055/s-0030-1270904
4. Cragg GM, Newman DJ. Natural products: a continuing source of novel drug leads. *Biochim. Biophys. Acta.* 2013;1830(6): 3670-3695. doi: 10.1016/j.bbagen.2013.02.008
5. Danciu Corina SC, Antal Diana, Alexandra Popescu, *et al.* An Update on natural compounds and their modern formulations for the management of malignant melanoma. In: Badria FA, editor *Natural Products and Cancer Drug Discovery*. Intech.Open.2017; pp 42. doi: 10.5772/67647
6. Bhatt A. Phytopharmaceuticals: A new drug class regulated in India. *Perspect. Clin. Res.* 2016;7(2): 59-61. doi: 10.4103/2229- 3485.179435
7. Chinembiri TN, du Plessis LH, Gerber M, *et al.* Review of natural compounds for potential skin cancer treatment. *Molecules* 2014;19(8): 11679-11721. doi: 10.3390/molecules190811679
8. Candeias SM, Gaip US. The immune system in cancer prevention, development and therapy. *Anticancer Agents Med Chem* 2016;16(1): 101-107. doi: 10.2174/1871520615666150824153523
9. Ribatti D. The concept of immune surveillance against tumors. The first theories. *Oncotarget* 2017;8(4): 7175-7180. doi: 10.18632/oncotarget.12739
10. Burnet FM. The concept of immunological surveillance. *Prog Exp Tumor Res* 1970;13: 1-27. doi: 10.1159/000386035
11. Dunn GP, Bruce AT, Ikeda H, *et al.* Cancer immunoediting: from immunosurveillance to tumor escape. *Nat. Immunol.* 2002;3(11): 991-998. doi: 10.1038/ni1102-991

12. Kaplan DH, Shankaran V, Dighe AS, *et al.* Demonstration of an interferon gammadependent tumor surveillance system in immunocompetent mice. *Proc. Natl. Acad. Sci. U. S. A.* 1998;95(13): 7556-7561. doi: 10.1073/pnas.95.13.7556
13. Shankaran V, Ikeda H, Bruce AT, *et al.* IFN $\gamma$  and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature* 2001;410(6832): 1107-1111. doi: 10.1038/35074122
14. Galluzzi L, Aaronson SA, Abrams J, *et al.* Guidelines for the use and interpretation of assays for monitoring cell death in higher eukaryotes. *Cell. Death. Differ.* 2009;16(8): 1093-1107. doi: 10.1038/cdd.2009.44
15. Ruggiero D. The role of Myc-induced protein synthesis in cancer. *Cancer. Res.* 2009;69(23): 8839-8843. doi: 10.1158/0008-5472.CAN09-1970
16. Green DR, Ferguson T, Zitvogel L, *et al.* Immunogenic and tolerogenic cell death. *Nat. Rev. Immunol.* 2009;9(5): 353-363. doi: 10.1038/nri2545
17. Zitvogel L, Kepp O, Kroemer G. Immune parameters affecting the efficacy of chemotherapeutic regimens. *Nat. Rev. Clin. Oncol.* 2010;8(3): 151-160. doi: 10.1038/nrclinonc.2010.223
18. Tesniere A, Apetoh L, Ghiringhelli F, *et al.* Immunogenic cancer cell death: a key-lock paradigm. *Curr. Opin. Immunol.* 2008;20(5): 504-511. doi: 10.1016/j.coi.2008.05.007
19. Kroemer G, Galluzzi L, Kepp O, *et al.* Immunogenic cell death in cancer therapy. *Annu. Rev. Immunol.* 2013;31: 51-72. doi: 10.1146/annurev-immunol-032712-100008
20. Obeid M, Tesniere A, Ghiringhelli F, *et al.* Calreticulin exposure dictates the immunogenicity of cancer cell death. *Nat. Med.* 2007;13(1): 54-61. doi: 10.1038/nm1523
21. Michaud M, Xie X, Bravo-San Pedro JM, *et al.* An autophagy-dependent anticancer immune response determines the efficacy of melanoma chemotherapy. *Oncoimmunology* 2014;3(7): e944047. doi: 10.4161/21624011.2014.944047
22. Ghiringhelli F, Apetoh L, Tesniere A, *et al.* Activation of the NLRP3 inflammasome in dendritic cells induces IL-1 $\beta$ -dependent adaptive immunity against tumors. *Nat. Med.* 2009;15(10): 1170-1178. doi: 10.1038/nm.2028
23. Garg AD, Krysko DV, Verfaillie T, *et al.* A novel pathway combining calreticulin exposure and ATP secretion in immunogenic cancer cell death. *EMBO. J.* 2012;31(5): 1062-1079. doi: 10.1038/emboj.2011.497
24. Apetoh L, Ghiringhelli F, Tesniere A, *et al.* Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat Med* 2007;13(9): 1050-1059. doi: 10.1038/nm1622
25. Shiratsuchi A, Watanabe I, Takeuchi O, *et al.* Inhibitory effect of Toll-like receptor 4 on fusion between phagosomes and endosomes/lysosomes in macrophages. *J. Immunol.* 2014;172(4): 2039- 2047. doi: 10.4049/jimmunol.172.4.2039

26. Tesniere A, Panaretakis T, Kepp O, *et al.* Molecular characteristics of immunogenic cancer cell death. *Cell. Death. Differ.* 2018;15(1): 3-12. doi: 10.1038/sj.cdd.4402269
27. Chaput N, De Botton S, Obeid M, *et al.* Molecular determinants of immunogenic cell death: surface exposure of calreticulin makes the difference. *J. Mol. Med.* 2007;85(10): 1069-1076. doi: 10.1007/s00109-007-0214-1
28. Obeid M, Tesniere A, Panaretakis T, *et al.* Ecto-calreticulin in immunogenic chemotherapy. *Immunol. Rev.* 2007;220: 22-34. doi: 10.1111/j.1600-065X.2007.00567.x
29. Bezu L, Sauvat A, Humeau J, *et al.* eIF2alpha phosphorylation: A hallmark of immunogenic cell death. *Oncoimmunology* 2018;7(6): e1431089. doi: 10.1080/2162402X.2018.1431089
30. Nikesitch N, Lee JM, Ling S, *et al.* Endoplasmic reticulum stress in the development of multiple myeloma and drug resistance. *Clin. Transl. Immunology* 2018;7(1): e1007. doi: 10.1002/cti2.1007
31. Corazzari M, Gagliardi M, Fimia GM, *et al.* Endoplasmic reticulum stress, unfolded protein response, and cancer cell fate. *Front Oncol* 7: 78. doi: 10.3389/fonc.2017.00078
32. Madden E, Logue SE, Healy SJ, *et al.* The role of the unfolded protein response in cancer progression: From oncogenesis to chemoresistance. *Biol. Cell.* 2019;111(1): 1-17. doi: 10.1111/boc.201800050
33. Staniforth V, Wang SY, Shyur LF, *et al.* Shikonins, phytochemicals from *Lithospermum erythrorhizon*, inhibit the transcriptional activation of human tumor necrosis factor alpha promoter in vivo. *J. Biol. Chem.* 2017;279(7): 5877-5885. doi: 10.1074/jbc.M309185200
34. Su PF, Staniforth V, Li CJ, *et al.* Immunomodulatory effects of phytochemicals characterized by in vivo transgenic human GM-CSF promoter activity in skin tissues. *J. Biomed. Sci.* 2008;15(6): 813-822. doi: 10.1007/s11373-008-9266-7
35. Chiu SC, Yang NS. Inhibition of tumor necrosis factor- $\alpha$  through selective blockade of Pre-mRNA splicing by shikonin. *Mol. Pharmacol.* 2007;71(6): 1640-1645. doi: 10.1124/mol.106.032821
36. Chen HM, Wang PH, Chen SS, *et al.* Shikonin induces immunogenic cell death in tumor cells and enhances dendritic cell-based cancer vaccine. *Cancer. Immunol Immunother.* 2012;61(11): 1989-2002. doi: 10.1007/s00262-012-1258-9
37. Yin SY, Efferth T, Jian FY, *et al.* Immunogenicity of mammary tumor cells can be induced by shikonin via direct binding-interference with hnRNPA1. *Oncotarget* 2016;7(28): 43629-43653. doi: 10.18632/oncotarget.9660
38. Garg AD, Vandenberk L, Koks C, *et al.* Dendritic cell vaccines based on immunogenic cell death elicit danger signals and T cell-driven rejection of high-grade glioma. *Sci. Transl. Med.* 2016;8(328): 328ra327. doi: 10.1126/scitranslmed.aae0105

39. Krysko DV, Garg AD, Kaczmarek A, *et al.* Immunogenic cell death and DAMPs in cancer therapy. *Nat. Rev. Cancer.* 2012;12(12): 860-875. doi: 10.1038/nrc3380
40. Turrini E, Catanzaro E, Muraro MG, *et al.* Hemidesmus indicus induces immunogenic death in human colorectal cancer cells. *Oncotarget* 2018;9(36): 24443-24456. doi: 10.18632/oncotarget.25325
41. Castaneda DM, Pombo LM, Uruena CP, *et al.* A gallotannin-rich fraction from *Caesalpinia spinosa* (Molina) Kuntze displays cytotoxic activity and raises sensitivity to doxorubicin in a leukemia cell line. *BMC. Complement. Altern. Med.* 2012;12: 38. doi: 10.1186/1472-6882-12-38
42. Uruena C, Gomez A, Sandoval T, *et al.* Multifunctional T lymphocytes generated after therapy with an antitumor gallotannin-rich normalized fraction are related to primary tumor size reduction in a breast cancer model. *Integr. Cancer. Ther.* 2015;14(5): 468-483. doi: 10.1177/1534735415596425
43. Gomez-Cadena A, Uruena C, Prieto K, *et al.* Immune-system dependent anti-tumor activity of a plant-derived polyphenol rich fraction in a melanoma mouse model. *Cell. Death. Dis.* 2016;7(6): e2243. doi: 10.1038/cddis.2016.134
44. Prieto K, Cao Y, Mohamed E, *et al.* Polyphenol-rich extract induces apoptosis with immunogenic markers in melanoma cells through the ER stress-associated kinase PERK. *Cell. Death. Discov* 2019;5: 134. doi: 10.1038/s41420-019-0214-2
45. Ren Y, Wei M, Still PC, *et al.* Synthesis and antitumor activity of ellagic acid peracetate. *ACS. Med. Chem. Lett* 2012;3(8): 631-636. doi: 10.1021/ml300065z
46. Li X, Dong W, Nalin AP, *et al.* The natural product chitosan enhances the anti-tumor activity of natural killer cells by activating dendritic cells. *Oncoimmunology* 2018;7(6): e1431085. doi: 10.1080/2162402X.2018.1431085
47. Deng Y, Chu J, Ren Y, *et al.* The natural product phyllanthusmin C enhances IFN-gamma production by human NK cells through upregulation of TLR-mediated NF-kappaB signaling. *J. Immunol* 2014;193(6): 2994-3002. doi: 10.4049/jimmunol.1302600
48. Kunnumakkara AB, Anand P, Aggarwal B. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer. Lett.* 2008;269(2): 199-225. doi: 10.1016/j.canlet.2008.03.009
49. Chang YF, Chuang HY, Hsu CH, *et al.* Immunomodulation of curcumin on adoptive therapy with T cell functional imaging in mice. *Cancer. Prev. Res. (Phila)* 2012;5(3): 444-452. doi: 10.1158/1940-6207.CAPR-11-0308
50. Dai Y, Kato M, Takeda K, *et al.* T-cell-immunity-based inhibitory effects of orally administered herbal medicine juzen-taiho-to on the growth of primarily developed melanocytic tumors in RET-transgenic mice. *J. Invest. Dermatol.* 2001;117(3): 694-701. doi: 10.1046/j.0022-202x.2001.01457.x

51. Foster K, Younger N, Aiken W, *et al.* Reliance on medicinal plant therapy among cancer patients in Jamaica. *Cancer Causes Control* 2017;28(11): 1349-1356. doi: 10.1007/s10552-017-0924-9
52. Hernandez JF, Uruena CP, Cifuentes MC, *et al.* A *Petiveria alliacea* standardized fraction induces breast adenocarcinoma cell death by modulating glycolytic metabolism. *J.Ethnopharmacol* 2014;153(3): 641-649. doi: 10.1016/j.jep.2014.03.013
53. John F.Hernández CPU, Tito A.Sandoval, Maria C.Cifuentes, *et al.* A cytotoxic *Petiveria alliacea* dry extract induces ATP depletion and decreases  $\beta$ F1-ATPase expression in breast cancer cells and promotes survival in tumor-bearing mice. *Revista Brasileira de Farmacognosia* 2017;27(3): 306- 314. doi: 10.1016/j.bjp.2016.09.008
54. Junio HA, Sy-Cordero AA, Ettefagh KA, *et al.* Synergy-directed fractionation of botanical medicines: a case study with goldenseal (*Hydrastis canadensis*). *J. Nat. Prod.* 2011;74(7): 1621-1629. doi: 10.1021/np200336g
55. Ettefagh KA, Burns JT, *et al.* Goldenseal (*Hydrastis canadensis* L.) extracts synergistically enhance the antibacterial activity of berberine via efflux pump inhibition. *Planta. Med* 2011;77(8): 835-840. doi: 10.1055/s-0030-1250606
56. Lovelace ES, Polyak SJ. Natural products as tools for defining how cellular metabolism influences cellular immune and inflammatory function during chronic infection. *Viruses* 2015;7(12): 6218- 6232. doi: 10.3390/v7122933
57. Bolognesi ML, Budriesi R, Chiarini A, *et al.* Design, synthesis, and biological activity of prazosin-related antagonists. Role of the piperazine and furan units of prazosin on the selectivity for alpha1-adrenoreceptor subtypes. *J. Med. Chem.* 1998;41(24): 4844-4853. doi: 10.1021/jm9810654
58. Melchiorre C, Andrisano V, Bolognesi ML, *et al.* Acetylcholinesterase noncovalent inhibitors based on a polyamine backbone for potential use against Alzheimer's disease. *J. Med. Chem* 1998;41(22): 4186-4189. doi: 10.1021/jm9810452
59. Bolognesi ML, Cavalli A. Multitarget drug discovery and polypharmacology. *Chem.Med.Chem* 2016;11(12): 1190-1192. doi: 10.1002/cmdc.201600161
60. Wing Lam SB, Fulan Guan, Zaoli Jiang, *et al.* The four-herb Chinese medicine PHY906 reduces chemotherapy-induced gastrointestinal toxicity *science translational medicine* 2010;2(45): 45ra59. doi: 10.1126/scitranslmed.3001270
61. Gatti A, Sabato E, Di Paolo AR, *et al.* Oxycodone/paracetamol: A low-dose synergic combination useful in different types of pain. *Clin. Drug. Investig.* 2010;30 (Suppl 2): 3-14. doi: 10.2165/1158414-S0-000000000-00000
62. Chung J, DiGiusto DL, Rossi JJ. Combinatorial RNA-based gene therapy for the treatment of HIV/AIDS. *Expert. Opin. Biol. Ther.* 2013;13(3): 437-445. doi: 10.1517/14712598.2013.761968



63. Pirrone V, Thakkar N, Jacobson JM, *et al.* Combinatorial approaches to the prevention and treatment of HIV-1 infection. *Antimicrob Agents Chemother* 2001;55(5): 1831-1842. doi: 10.1128/AAC.00976-10
64. Nanayakkara AK, Follit CA, Chen G, *et al.* Targeted inhibitors of P-glycoprotein increase chemotherapeutic-induced mortality of multidrug resistant tumor cells. *Sci. Rep* 2018;8(1): 967. doi: 10.1038/s41598-018-19325-x
65. Mukhtar H, Ahmad N. Tea polyphenols: prevention of cancer and optimizing health. *Am J. Clin. Nutr* 2000;71(6 Suppl): 1698S-1702S; discussion 1703S-1694S. doi: 10.1093/ajcn/71.6.1698S
66. Shimizu M, Deguchi A, Lim JT, *et al.* (-)-Epigallocatechin gallate and polyphenon E inhibit growth and activation of the epidermal growth factor receptor and human epidermal growth factor receptor-2 signaling pathways in human colon cancer cells. *Clin. Cancer. Res.* 2005;11(7): 2735-2746. doi: 10.1158/1078-0432.CCR-04-2014
67. Lambert JD, Hong J, Yang GY, *et al.* Inhibition of carcinogenesis by polyphenols: evidence from laboratory investigations. *Am. J. Clin. Nutr.* 2005;81(1 Suppl): 284S-291S. doi: 10.1093/ajcn/81.1.284S
68. Nam S, Smith DM, Dou Q. Ester bond-containing tea polyphenols potently inhibit proteasome activity in vitro and in vivo. *J. Biol. Chem* 2001;276(16): 13322-13330. doi: 10.1074/jbc.M004209200
69. Adhami VM, Siddiqui IA, Ahmad N, *et al.* Oral consumption of green tea polyphenols inhibits insulin-like growth factor-I-induced signaling in an autochthonous mouse model of prostate cancer. *Cancer. Res.* 2004;64(23): 8715-8722. doi: 10.1158/0008-5472.CAN-04-2840
70. Moreira R, Pereira DM, Valentao P, *et al.* Pyrrolizidine alkaloids: Chemistry, pharmacology, toxicology and food safety. *Int. J. Mol. Sci.* 2018;19(6): E1668. doi: 10.3390/ijms19061668
71. Nortier JL, Martinez MC, Schmeiser HH, *et al.* Urothelial carcinoma associated with the use of a Chinese herb (*Aristolochia fangchi*). *N. Engl. J. Med.* 2000;342(23): 1686-1692. doi: 10.1056/NEJM200006083422301
72. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol* 2014;4: 177. doi: 10.3389/fphar.2013.00177
73. Lasso P, Gomez-Cadena A, Uruena C, *et al.* Prophylactic vs. therapeutic treatment with P2Et polyphenol-rich extract has opposite effects on tumor growth. *Front. Oncol.* 2018;8: 356. doi: 10.3389/fonc.2018.00356
74. Barabasi AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nat. Rev. Genet.* 2011;12(1): 56- 68. doi: 10.1038/nrg2918
75. Mencher SK, Wang LG. Promiscuous drugs compared to selective drugs (promiscuity can be a virtue). *BMC. Clin. Pharmacol.* 2005;5: 3. doi: 10.1186/1472-6904-5-3
76. Poornima P, Kumar JD, Zhao Q, *et al.* Network pharmacology of cancer: From understanding of complex interactomes to the design of multi-target specific therapeutics from nature. *Pharmacol. Res* 2016;111: 290-302. doi: 10.1016/j.phrs.2016.06.018

77. Fan X, Zhao X, Jin Y, *et al.* Network toxicology and its application to traditional Chinese medicine. *Zhongguo. Zhong. Yao. Za. Zhi* 2001;36(21): 2920-2922. PMID: 22308674
78. Lee AY, Park W, Kang TW, *et al.* Network pharmacology-based prediction of active compounds and molecular targets in Yijin-Tang acting on hyperlipidaemia and atherosclerosis. *J. Ethnopharmacol* 2018;221: 151-159. doi: 10.1016/j.jep.2018.04.027
79. Zhang S, Shan L, Li Q, *et al.* Systematic analysis of the multiple bioactivities of green tea through a network pharmacology approach. *Evid Based Complement Alternat Med* 2014: 512081. doi: 10.1155/2014/512081
80. Gao L, Wang XD, Niu YY, *et al.* Molecular targets of Chinese herbs: a clinical study of hepatoma based on network pharmacology. *Sci. Rep* 2016;6: 24944. doi: 10.1038/srep24944
81. Ramsay RR, Popovic-Nikolic MR, *et al.* A perspective on multi-target drug discovery and design for complex diseases. *Clin. Transl. Med* 2018;7(1): 3. doi: 10.1186/s40169-017-0181-2
82. Yildirim MA, Goh KI, Cusick ME, *et al.* Drug target network. *Nat. Biotechnol* 2007;25(10): 1119-1126. doi: 10.1038/nbt1338
83. Cavalli A, Bolognesi ML, Minarini A, *et al.* Multi-target-directed ligands to combat neurodegenerative diseases. *J. Med. Chem.* 2008;51(3): 347-372. doi: 10.1021/jm7009364
84. Liu Z, Du J, Yan X, *et al.* TCM analyzer: A chemo- and bioinformatics web service for analyzing traditional Chinese medicine. *J. Chem. Inf. Model.* 2018;58(3): 550-555. doi: 10.1021/acs.jcim.7b00549
85. Wong YH, Lin CL, Chen TS, *et al.* Multiple target drug cocktail design for attacking the core network markers of four cancers using ligand-based and structure-based virtual screening methods. *B.M.C Med. Genomics* 2015;8 (4): S4. doi: 10.1186/1755-8794-8-S4-S4
86. Kepp O, Menger L, Vacchelli E, *et al.* Crosstalk between ER stress and immunogenic cell death. *Cytokine Growth. Facto. Rev.* 2013;24(4): 311-318. doi: 10.1016/j.cytogfr.2013.05.001