Network Pharmacology of Ayurveda Formulation *Triphala* with Special Reference to Anti-Cancer Property

Uma Chandran¹, Neelay Mehmendale², Girish Tillu¹ and Bhushan Patwardhan *¹

¹Interdisciplinary School of Health Sciences, ²Institute of Bioinformatics and Biotechnology, Savitribai Phule Pune University, Pune, India

Abstract: Network pharmacology is an emerging technique, which integrates systems biology and computational biology to study multi-component and multi-targeted formulations. Ayurveda, the traditional system of Indian medicine, uses intelligent formulations; however, their scientific rationale and mechanisms remain largely unexplored. This paper presents the potential of network pharmacology to understand the rationale of a commonly used Ayurveda formulation known as *Triphala*. We have developed pharmacology networks of Triphala based on the information gathered from different databases and using the software Cytoscape. The networks depict the interaction of bioactives with molecular targets and their relation with diseases, especially cancer. The network pharmacology analysis of *Triphala* has offered new relationships among bioactives, targets and putative applications of cancer etiology. This pioneering effort might open new possibilities to know pharmacodynamics of Ayurvedic drugs like *Triphala* and also help in the discovery of new leads and targets for various diseases.

Keywords: Ayurveda, bioactives, drug discovery, drug targets, network pharmacology, systems biology, *Triphala*.

INTRODUCTION

The natural and traditional medicines are reemerging as promising new leads, to boost new drug discovery. Combinatorial chemistry approaches based on natural product scaffolds are being used to create screening libraries of closely resembling drug-like compounds [1, 2]. Normally, drug discovery follows the one gene-one target-one drug track; however, a multi-target, multi-ingredient formulation approach may be the smarter approach. It is important to address multiple targets emanating from a syndrome-related, metabolic cascade so that holistic management can be effectively achieved. Therefore, it is necessary to shift the strategy from one that focuses on a single target-new chemical entity as a drug, to one of a multiple-target, synergistic, formulation discovery approach [3].

Network pharmacology is an emerging discipline useful in formulation discovery, which integrates recent advances in omics technologies and systems biology through computational biology [4]. Current drug discovery attempts are being made to design ligands with maximum selectivity to act on specific drug targets. Like enzyme action, the drug-receptor relation is considered to be highly specific - like a “lock and key”. However, just as one master key can open many locks, many drugs may modulate multiple proteins, rather than acting upon single targets.

Many drugs used in specialties like oncology, cardiology and psychiatry, have effects on multiple targets. To better understand the underlying complex biological, and pharmacological processes for chronic diseases like asthma, cancer, and neurodegenerative diseases, it is important to know the systems network of different pathways where the drugs are likely to act [5]. For instance, cancer is a complex multi-gene dependent disease. A single drug that binds a single target is not as effective as a multi-drug formulation that binds multiple targets associated with the disease. By acting on multiple targets, the formulation regulates pathways that function in the diseased state [6]. A network of interactions between natural products and cancer target proteins helps to find out potential cancer drug leads and novel interactions [7]. Many diseases have a common genetic origin and so there is a need for drug repurposing [8].

AYURVEDA FORMULATIONS

Indian traditional medicine Ayurveda offers many sophisticated formulations, which have been used for hundreds of years. The Traditional Knowledge Digital Library (TKDL, http://www.tkdl.res.in) contains over 36,000 classical Ayurveda formulations. Out of these about 100 formulations are very popular and are being used even at the community level as over-the-counter products. Some of these drugs continue to be used as home remedy in India for preventive, and primary health care. *Triphala* is one of such popular Ayurveda formulations.

*Triphala* consists of pitted fruits, known as myrobalans, of three botanicals. The ingredient botanicals are *Emblica officinalis* (EO) also known as *Phyllanthus emblica*, commonly known as Indian gooseberry in English, or *Amalaki* in the vernacular; *Terminalia bellirica* (TB), known as *Bibhitaka*; and *Terminalia chebula* (TC), known as *Haritaki* in the vernacular. In *Triphala*, these myrobalans are normally used as a mixture consisting of an equal proportion of all the three. This combination has putative synergistic...
properties. *Triphala* is considered as a good *Rasayana*, which improves immunity and facilitates nourishment to tissues [9]. With antioxidant and anti-aging effects, it is used for strengthening the vital organs, for improving skin and hair quality, for diabetic wound management and as a general health promoter.

*Triphala* is a constituent of about 1500 Ayurveda formulations and it can be used for several diseases. *Triphala* is indicated for degenerative and metabolic disorders possibly through lipid peroxide inhibition and free radical scavenging [10]. In a phase I clinical trial on healthy volunteers, immunostimulatory effects of *Triphala* on cytotoxic T cells and natural killer cells have been reported [11]. *Triphala* is shown to induce apoptosis in tumor cells of the human pancreas, in both *in vitro* and *in vivo* models [12]. Although, the anticancer properties of *Triphala* have been studied, the exact mechanism of action is still not known. The doses, dosage forms and vehicle of administration may change as per the nature of symptom, individual *Prakriti* and state of the disease [3]. Therefore, we hypothesize that formulations like *Triphala* are intelligent formulations, which act based on the internal and external environments in which they are prepared and administered (Fig. 1).

Many Chinese researchers have employed network pharmacology to explore the pharmacological mechanisms of complex herbal formulations from Traditional Chinese Medicine (TCM) [13, 14]. Synergistic activity of TCM formulations like Qing-Luo-Yin and Liu-Wei-Di-Huang pill has been studied using network pharmacology [15]. Recently, the molecular mechanisms of TCM herbal formula known as Guizhi-Shaoyao-Zhimu used in the treatment of diabetic peripheral neuropathy have been investigated with network pharmacology [16]. The drug-target networks will expose ways to drug repositioning as well as uncovering novel drugs and targets, which can aid basic and clinical research [17,18]. However, there were no such studies carried out on Ayurvedic formulations. Recently, we have reported the application of this technique in understanding the underlying mechanism of Ayurveda formulation [19]. In this study, we have used network pharmacology as a tool to

![Fig. (1). Multi-dimensional effects of Triphala (Reproduced with permission from Patwardhan B, Mutalik G, Tillu G 2015. Integrative Approaches for Health. Elsevier).](image-url)
understand the pharmacodynamics of Triphala as an intelligent formulation, which can be used for several indications. The available information regarding bioactives of Triphala botanicals have been used to construct pharmacology networks involving putative targets and related diseases. As an example, we have performed a detailed analysis to show the potential of Triphala in cancer therapeutics.

MATERIALS AND METHODS

**Triphala, Bioactives and Targets**

The reported bioactive compounds from three botanicals present in *Triphala* are used to construct pharmacology networks. The structural information of bioactives were retrieved from the Universal Natural Products Database (UNPD) [20] in the ‘.sdf’ format. All the available UNPD structures of the bioactives were used for the study including various conformations. The ‘.sdf’ files having the structures of the bioactives were queried in Binding database or ‘Binding DB’ for identifying their targets using special tool ‘find my compounds’ target’ [21]. Binding DB is a web based free database that covers protein interactions with small drug-like molecules. It searches for the exact or similar compounds in the database and retrieves the target information of those compounds. The similarity search gives the structurally similar compounds with the degree of similarity to the queried structure as scores, where 1 is the highest possible value. A score of 1 indicates that either the exact queried compound is present or it gives a 100% structural similarity to another compound in the database. We compiled data for similarity search greater than/equal to 0.7. The targets of those bioactives having a score equal to 1 were selected to improve the accuracy of results (Supplementary Table S1).

The Binding DB is connected to numerous databases and these connections were used to extract further information regarding the targets. The protein and gene names were taken from UniProt [22] using the UniProt IDs. Binding DB also allowed for fetching information regarding the type of target, mode of action of the bioactive (i.e. activation or inhibition), the source organism and the chemical entity that the bioactive is being compared to. The database also links ‘Reactome’, a curated pathway database [23]. Reactome was used to find the pathways involved in the targets, function.

**Disease Types and Indications**

The targets of the bioactives were searched in the Therapeutic Targets Database (TTD) [24] for their association with any disease or indication. The diseases were clustered into classified disease types using the Disease and Gene Annotation (DGA), a tool that provides a comprehensive and integrative annotation of human genes in disease networks [25].

**Network Construction**

A pharmacology network is made up of nodes, the points of communication or redistribution, and edges, the lines of communication joining the nodes. The entities that form the nodes of the networks are three constituent botanicals (EO, TB and TC) of *Triphala* networked with their bioactive compounds, related targets, relevant diseases and the underlying pathways. The networks were constructed using Cytoscape 3.2.1, a java based open source software [26]. The tools available in Cytoscape were used for analyzing the networks.

The *Triphala* network links its botanical constituents, bioactives, targets and the associated diseases in the respective series. The possible duplicates of the bioactives were eliminated while constructing the networks. We have constructed a subset network of *Triphala* and cancer to demonstrate the utility of pharmacology networks in cancer therapeutics.

**RESULTS**

**Triphala - Bioactive - Target Network**

The botanicals of *Triphala* - EO, TB and TC contain 122, 34 and 63 bioactives respectively according to UNPD data collected on March 2015. Of these, a few bioactives are common among the three botanicals. Thus, *Triphala* formulation as a whole contains 194 bioactives. Out of these, 25 bioactives were Score-1 based on Binding DB search carried out on March-April 2015. EO, TB and TC contain 18, 5 and 11 Score-1 bioactives respectively (Fig. 2). The Score-1 bioactives which are common among the three botanicals are chebulanic, ellagic acid, 1, 2, 3, 4, 6-pentagalloylglucose and tannic acid.

Twenty five Score1 bioactives of *Triphala* are shown to interact with 45 human protein targets in 74 possible combinations (Supplementary Table S2). Quercetin, ellagic acid, 1,2,3,4,6-pentagalloylglucose and 1,2,3,6-tetrakis(O-galloyl)-beta-D-glucose are the four bioactives which interact with the maximum number of targets; 11, 10, 7 and 7 respectively. *Triphala* bioactives are found to be acting by inhibiting 46 targets out of 74 bioactive-target interactions, while in 7 they are activating and in rest 21 the action is still unknown. The data shows that ellagic acid and quercetin inhibit the most number of target proteins, 10 and 9 respectively. Whereas, 1,2,3,4,6-pentagalloylglucose, 1,2,3,6-tetrakis(O-galloyl)-beta-D-glucose and punicalins activate target proteins. The major targets which are inhibited include insulin receptor (INSR), beta-secretase 1 (BACE1), cytochrome P450 (CYP), serine/ threonineprotein kinase (PIM1) and tissue-type plasminogen activator (PLAT). The proteins which are activated include glutathione S-transferase (GSTA1), regulator of G-protein signaling (RGS) RGS4, RGS7 and RGS8.

**Triphala-Disease Network**

A network of *Triphala*-disease shows that *Triphala* can act against 15 disease types involving 74 different disease indications through modulation of 31 protein targets (Fig. 3). The major disease types in which *Triphala* is networked are cancer, cardiovascular system disease, neurodegenerative disorders and metabolic disorders (Supplementary Table S3). Ellagic acid, quercetin, 1,2,3,4,6-pentagalloylglucose, 1,2,3,6-tetrakis(O-galloyl)-beta-D-glucose and epigallocatechin 3-gallate are the bioactives
which are connected to multiple disease types. Our results indicate that 13 bioactives can interact with 17 targets in 27 combinations suggesting a link to cancer. Ten bioactives can modulate 7 targets related to nervous system disorders in 16 combinations. Triphala can regulate cardiovascular disorders through 9 bioactives which can interact in 12 combinations with 7 targets. Five bioactives are interacting with 6 targets of metabolic diseases in 9 combinations. The protein targets of Triphala bioactives are also involved in respiratory system diseases, bleeding disorders, gastrointestinal diseases, urinary diseases, musculoskeletal diseases and parasitic infections.

The specific cardiovascular indications in which Triphala is connected include thrombotic diseases, atrial fibrillation and flutter, coronary heart disease and atherosclerosis. Major bioactives taking part in cardiovascular indications include 1,2,3,4,6-Pentagalloylglucose, 1,2,3,6-tetrakis(O-galloyl)-beta-D-glucose, 2sitosterol and casuarinin. The targets through which Triphala may regulate cardiovascular system are Factor Xa (F10), Fatty acid binding protein adipocyte (FABP4), HMG-CoA reductase (HMGCR), NADPH oxidase 4 (NOX4), Placenta growth factor (PGF), Plasminogen activator inhibitor 1 (SERPINE1) and Sterol regulatory element-binding protein 2 (SREBP2). Triphala can also be useful in few nervous system diseases such as Alzheimer's disease, dementia, age-related macular degeneration and diabetic retinopathy, which are linked through 1,2,3,4,6-Pentagalloylglucose, 1,2,3,6-tetrakis(O-galloyl)-beta-D-glucose, ellagic acid, epigallocatechin 3-gallate and quercetin. Major metabolic disease indications that can be controlled with Triphala include diabetes mellitus, obesity and hypercholesterolemia mainly through 2sitosterol, quercetin, ellagic acid and lauric acid.

**Triphala-Cancer Network**

The subnetwork of Triphala-cancer developed with cancer types, bioactives, targets and their pathway of interaction as nodes indicates that Triphala is involved in 24 different types of cancers (Fig. 4). This linkage is through the interaction of 13 bioactives and 17 target proteins in 27 different bioactive-target combinations. The types of cancers which are networked by Triphala include pancreatic, prostate, breast, lung, colorectal, and gastric cancers and tumors (Supplementary Table S4). Triphala is linked to pancreatic cancer through interactions of 8 bioactives with 4 targets; BACE1, carbonic anhydrase (CA) CA2, CA6 and hepatocyte growth factor (HGF) in 9 different combinations. The major bioactives involved in this are 1,2,3-benzenetriol, ellagic acid, epigallocatechin 3-gallate, punicalagin and

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**Fig. (2). Triphala: bioactive-target network. EO, TB and TC are the botanicals. Oval nodes are the bioactives in which black colour represents the score 1 bioactives whereas grey colour represents the bioactives below Score-1. Targets are represented by diamond nodes in which labels I, A and U represent inhibited, activated and unknown modulation respectively.**
quercetin. CA2 and CA6 are functioning by reversible hydration of carbon dioxide whereas HGF by sema4D mediated inhibition of cell attachment and migration. The network of Triphala with prostate cancer shows the interaction of four bioactives ellagic acid, quercetin, epigallocatechin 3-gallate and kaempferol; with three targets CYP1B1, HGF and telomerase reverse transcriptase (TERT). These proteins are acting through N-hydroxylation or N-dealkylation of aromatic amines, sema4D mediated inhibition of cell attachment and migration pathways, and telomere extension by telomerase respectively.

Ellagic acid, kaempferol and quercetin from Triphala can interact with SRC and CYP1B1 which are candidate proteins of breast cancer. The signaling pathways through which proteins are acting involve ERBB2 and N-hydroxylation or N-dealkylation of aromatic amines. The interaction of ellagic

Fig. (3). Triphala-disease network. Oval nodes are the Score1 bioactives. Targets are represented by diamond nodes in which labels I, A and U nodes represent inhibited, activated and unknown modulation respectively. Octagon nodes and triangle nodes represent disease types and indications respectively.
Kapha

Ayurveda describes three physical, physiological and psychological functions. Its properties (DISCUSSION) mediated inhibition of cell attachment and migration, SHC-TRIPELA, CYP1B1, TERT and SRC are the targets through which Sema4D is linked to multiple cancer indications. Sema4D mediated inhibition of cell attachment and migration, SHC-related events triggered by IGFR1 and N-hydroxylation or N-dealkylation of aromatic amines are the major pathways through which targets of Tripbala bioactives are acting.

Fig. (4). Tripbala-cancer network. Triangle nodes represent cancer indications. Oval nodes are the Score1 bioactives. Targets are represented by diamond nodes with target names in which labels I, A and U represent inhibited, activated and unknown modulation respectively. Octagon nodes represent molecular pathways.

From the Tripbala-cancer network, it is inferred that ellagic acid, quercetin and epigallocatechin 3-gallate play a major role in connecting Tripbala with cancer. HGF, IGFR1, CYP1B1, TERT and SRC are the targets through which Tripbala is linked to multiple cancer indications. Sema4D mediated inhibition of cell attachment and migration, SHC-related events triggered by IGFR1 and N-hydroxylation or N-dealkylation of aromatic amines are the major pathways through which targets of Tripbala bioactives are acting.

DISCUSSION

Ayurveda describes any substance (Dravya) in terms of its properties (Guna), activities (Karma) and indications in specific diseases. According to Ayurveda constructs, Doshas are the dynamic principles, which govern a person’s physical, physiological and psychological functions. Ayurveda describes three Doshas namely Vata, Pitta, and Kapha [27]. The complex relations among these variables are strikingly similar to modern understanding of pharmacology networks of bioactives, targets and diseases.

Tripbala, an antioxidant rich formulation, is considered as an effective medicine for restoring health by balancing all the three Doshas - Kapha, Pitta and Vata. It is supposed to improve immunity, arrest degeneration and aging, and nourish tissues. It is a drug of choice for many health conditions such as digestive diseases, metabolic disorders, dental and skin diseases, cataracts, conjunctivitis, wound healing and liver diseases. Tripbala has also been used as a bowel regulator, laxative, diuretic, blood purifier and general tonic [28]. Many studies have shown that Tripbala is useful in the prevention of cancer and possesses antineoplastic, radioprotective and chemoprotective effects [29].

We found that according to available data, Tripbala formulation contains 194 bioactives. For the accuracy of analysis, we focused on the Score1 bioactives based on Binding DB results. We report that 25 bioactives are giving interaction with 45 human protein targets in 74 different combinations. These 45 targets are linked to 15 disease types which in turn are associated with 74 indications. Thus, the network analysis indicates that Tripbala can be effective for 74 different disease indications.

Multi-targeting is a unique characteristic of botanical formulations [30]. The bioactive-target network depicts the multi-targeting property of Tripbala. In addition to this, some proteins are targeted by multiple bioactives. In Tripbala network, the proteins that are targeted by maximum number of bioactives are BACE1, carbonic anhydrase (CA) VII (CA7), RGS7 and RGS8, those are targeted by four bioactives each. The four bioactives; epigallocatechin 3-gallate, punicalagin, terflavin A and terflavin C are known to inhibit the target BACE1 [31-33]. Though, catechin, epicatechin, galloycatechin and trans-3,3',4,5,7-pentahydroxylflavane are shown to interact with the target, CA7, the mode of action is not yet studied [34]. RGS7 is targeted by 1,2,3,4,6-pentagalloylgucose, 1,2,3,6-tetraakis(O-galloyl)-beta-D-glucose, chebulanin and chebulinic acid, where the first two bioactives are activating the target. The mode of action of the last two bioactives is not known [35]. Chebulanin, chebulinic acid, punicalins and terflavin B are shown to interact with RGS8. But except punicalins, which is an activator, all other bioactives’ mode of action is not known [36].

Among the disease types, cancer is networked most by Tripbala bioactives (Fig. 4). Thirteen different bioactives of Tripbala are linked to 24 different types of cancer indications through 17 targets by 27 bioactive-target combinations. In Tripbala-cancer network, the degree of interaction between bioactive and target is maximum for pancreatic cancer followed by prostate and breast cancers. Studies have shown that Tripbala induce apoptosis in human pancreatic cells through activation of ERK and p53 [12]. Our network data also show that Tripbala is linked to pancreatic cancer through the interaction of eight bioactives with four proteins CA2, CA6, BACE1 and HGF.

The anti-prostate cancer property of gallic acid has already been reported [37, 38]. Our network pharmacology analysis indicates that ellagic acid, epigallocatechin 3-
gallate, quercetin and kaempferol interact with targets TERT, CYP1B1 and HGF which are connected to prostate cancer.

Currently two drugs, ARQ 197 [39] and Cabozantinib [40], which are targeting HGF, are under phase II trial for pancreatic cancer and prostate cancer. Potential of ellagic acid as a radiosensitizer in breast cancer cell lines, MCF-7, has also been reported [41]. Antiproliferative effect of *Triphala* in breast cancer cell lines, MCF-7 and T47 D has shown the role of ROS in the induction of apoptosis [42]. Network analysis also illustrates the role of ellagic acid in breast cancer by inhibiting SRC. Bosutinib is a drug targeting SRC for advanced breast cancer, which is under phase II study [43]. The other two bioactives from our data that are linked to breast cancer are kaempferol and quercetin. Both are targeting CYP1B1. One of the bioactives of *Triphala*, chebulinic acid, has a putative role in inhibiting VEGF induced angiogenesis by suppressing VEGFR2 [44]. Our data suggest ellagic acid as another inhibitor of VEGFR2. Another bioactive prodelphinidin A-1 interacts with PGF which is associated with angiogenesis. Pharmacological network analysis of *Triphala* provides insight into unexplored bioactives as well as uncovering new targets, for cancer (Table 1).

### CONCLUSION

Thus, network pharmacology is an effective computing tool to understand the intelligence behind traditional medicine through systematic data mining, information synthesis and collating bioactives, targets, pathways and the associated indications. This may be a pragmatic application of systems biology that connects complex etiopathology and targets with enriched phytochemistry of natural products. Network pharmacology analysis of *Triphala* has offered new

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relationships between bioactives, targets and putative applications in new diseases with special reference to cancer. Such pharmacology network approach could be useful to rediscover the potential of traditional medicine, to obtain new drug leads from natural sources, to investigate unexplored molecular targets and to design experimental and clinical studies. The pharmacology network provides systems overview of pharma-omics of bioactives with newer insights to expedite drug discovery, clinical research and therapeutics. It further provides a comprehensive data-driven approach for natural product pharmacology where the whole is more than the sum of its parts.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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