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# Network Pharmacology–Based Approach to Explore Potential Targets of Punchaskar Churn on Constipation and Piles

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**ABSTRACT**
*Network pharmacology (NP), a brand-new field, seeks to understand how drugs perform and interact with a variety of targets. By providing an objective examination of prospective target spaces, network pharmacology seeks to identify new drug leads and targets as well as repurposing existing drug molecules for alternative therapeutic conditions. Throughout the past few decades, emphasis has been placed on multi-target and combinatorial medicines. These methods successfully treated complex disorders like piles and constipation by controlling the activity of the targets. Because the coordinated operation of various gene groups must be stopped, the majority of diseases cannot be effectively treated with a single gene target. The majority of cellular components interact with one another in order to operate properly, and the interactome is made up of all of these interactions. This interconnectivity demonstrates how a gene malfunction may not be limited to the gene product alone but may instead propagate throughout the network. Hence, the network-based approach to understanding disease mechanisms must serve as the basis for developing new drugs. Since these illnesses entail intricate biological machinery, certain systematic diseases, such as neurodegenerative disorders, cancer, and cardiovascular, cannot be effectively treated by the single gene target strategy. Medicines with a wide range of targets may be more potent. Multi-target medicines may be less vulnerable since the biological system cannot support many activities. In this paper, we will give an overview of recent advancements in methods for identifying drug target interactions and their use in the poly-pharmacology profile of the drug. Network pharmacology study is to identify bioactive compounds of panchaskar churn containing 4 herbs and their potential targets by using some In silico methods, our network pharmacological analysis of Panchaskar churn identified four herbs, 31 phytochemical constituents and 270 target genes associated to Constipation and Piles. Based on the results of Network Construction, we determined that effects of Panchaskar churn against Constipation and piles may be due to the ingredients of panchaskar churn i.e., Cassia angustifolia, Terminalia chebula, Foeniculum vulgare, can simultaneously target numerous genes.*
**Keywords:** Network Pharmacology, Constipation, Piles, *Panchaskar churn*

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## INTRODUCTION

Drug discovery has always adhered to the prevailing paradigm of "one gene, one medicine, one disease" and has mostly focused on creating incredibly selective ligands with minimal side effects [1]. So far, because new drug candidates lacked efficacy and safety, their clinical attrition rate could have been as high as 30% [2]. Large-scale functional genomics investigations have also shown that just 34% of single-gene knockouts resulted in illness or mortality, while many single-gene knockouts have no impact on phenotype [3]. Systems biology is a recent development in bioscience study that emphasises changing the entire biological system rather than just one individual molecular component [4]. The hunt for multitarget medications that act on biological networks as "magic shotguns" substitutes the corollary of rational drug design of "magic bullets" in network pharmacology, a system biology-based paradigm [5]. According to network biology study, eliminating individual nodes has little impact on the illness networks [6]. The prevalent idea of single-target drug discovery is challenged by the growing awareness of the importance of network biology systems [7].

A new discipline called Network pharmacology (NP) has emerged which attempts to understand drug actions and interactions with multiple targets. Network pharmacology (NP), a new field of study that seeks to understand the effects and interactions of drugs with many targets [8]. The systematic cataloguing of a drug molecule's molecular interactions within a live cell makes use of computing capability. NP emerged

as a crucial tool for comprehending the intricate connections between plant remedies and the entire body [9].

As it emerges systematic medicine with information science, network pharmacology is developing as a new frontier in drug discovery and development [10]. By enabling an objective assessment of prospective target areas, it also seeks to identify novel drug leads and targets and to repurpose current drug molecules for various therapeutic diseases [11]. To choose the appropriate targets and fresh therapeutic molecule scaffolds, these efforts need some direction. Classical knowledge may be quite useful in the process of formulating new pharmaceuticals and reusing those that already exist. The next generation of promiscuous medications may be intelligently designed by fusing systems biology with NP breakthroughs [12].The goal of NP analysis is to increase the safety and effectiveness of already prescribed drugs in addition to providing novel treatment choices.

Constipation is a condition that affects the gastrointestinal tract and can cause painful, stiff, and infrequent faeces. Acute constipation may cause the bowel to close, necessitating surgery in some cases [13]. It is important to remember that there is no perfect description for constipation, therefore a history and physical exam can be thought of as the primary starting methods. Using a self-reported constipation and the formal criteria, many classifications are described. Scientific concepts like secondary reasons (medications), neurological disorders, or systemic illnesses are often mentioned in descriptions of chronic constipation. It is, nevertheless, regarded as primary or idiopathic [13]. Pathogenesis is multifaceted, with emphasis on factors such as genetic susceptibility, socioeconomic level, insufficient fibre intake, inadequate fluid intake, immobility, disruption of the hormone balance, drug side effects, or body structure, among others [13]. Constipation is a frequent gastrointestinal issue that costs the community a lot of money. Its prevalence is estimated to range from 1% to 80% worldwide and the disorder exhibits significant geographic variation. Significantly, different definitions have resulted in different levels of prevalence [14]. Age-related chronic constipation, which is characterised by challenging stools passage, is a complex disorder. This condition is closely related to the patients' quality of life and the use of healthcare resources [15]. To better understand the pathophysiology of chronic constipation, we set out to conduct an integrative review of the literature. A thorough grasp of this condition can help with illness management and therapy planning.

Hemorrhoids are defined as the symptomatic enlargement and distal displacement of the normal anal cushions. The most common symptom of hemorrhoids is rectal bleeding associated with bowel movement. The abnormal dilatation and distortion of the vascular channel, together with destructive changes in the supporting connective tissue within the anal cushion, is a paramount finding of hemorrhoids [16]. They are a significant medical and economical issue that affects millions of people worldwide. The development of piles has been linked to a number of causes, including constipation and prolonged straining. One of the most important symptoms of piles illness is the aberrant dilatation and distortion of the vascular channel together with damaging alterations in the supporting connective tissue within the anal cushion [17].

According to the Indian Ayurveda prescription, Panchsakar Churna (PC) is comprised of four herbs: Senna Patta (*Cassia angustifolia*) (Leaf), Bhuni Choti Harre (*Terminalia Chebula*) (Fruit), Sonth (*Zingiber Officinale*) (Rhizome), Sounf (*Foeniculum Vulgare*) (Fruit) and rock salt. It is used to enhance digestion and ensure prompt stool evacuation, as well as treat rheumatic conditions, haemorrhoids, Piles, abdominal pain, flatulence, and assimilatory disorders. Many reports documenting negative health consequences inconsistent quality, efficacy, and contents of herbal products have also been produced as a result of the growing popularity of herbal products as food, food supplements, and phytotherapeutic medications [2]. The use of this product is also mentioned in ancient literature such as Siddh Bheshaj Manimala, Udavartadhikara, and Rastantra Saar. All the ingredients of the Panchsakara Churn, including *Zingiber officinale*, *Foeniculum vulgare*, *Cassia angustifolia*, and *Terminalia chebula*, have been recommended for use in udararoga since ancient times. So, the main aim of the present study was designed to construct network for the identification of bioactive compounds and the targets of panchaskar churn on Constipation and Piles.

**Table 1: Formulation of *Panchaskar churn***

| S.NO | COMPOSITION |
|---|---|
| 1 | *Cassia angustifolia* |
| 2 | *Terminalia chebula* |
| 3 | *Foeniculum vulgare* |
| 4 | *Zingiber officinale* |

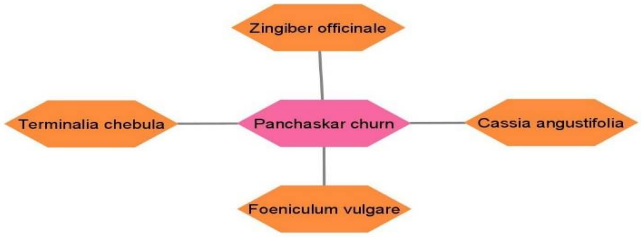


**Fig 01: Formulation of *Panchaskar churn***

## MATERIAL AND METHODS

### Search Strategy

The literature search was performed in PubMed. The search language was restricted to English. The search terms used were NP-related terms ("network pharmacology" OR "network analysis" OR "system-level" OR "systems-level" OR "systems pharmacology" OR "systems biology" OR "bioinformatics") and THM (Traditional Herbal Medicine)-related terms ("oriental medicine" OR "traditional medicine" OR "Traditional Asian medicine" OR "Chinese medicine" OR "Kampo medicine" OR "Korean medicine"). The search range of THM-related terms was extended to [title/abstract] since the titles of THM studies generally contain only the name of herbs or herbal formulae that are difficult to search [18].

### Inclusion Criteria

We considered a THM-NP study as the original article that analyzed a THM's mode of action through the construction of a compound-target network. Full-text articles from the literature search were checked to determine their eligibility. There was no restriction regarding *in vivo, in vitro*, and *in silico* studies. THM was considered as (1) extract(s) from a single herb; (2) preparation(s) containing multiple herbs; (3) proprietary herbal product(s); and (4) molecule(s) derived from a single herb [18].

### Data Extraction

Authors extracted the following data from the included THM-NP studies: authors, affiliations, publication years, tools, and databases. Synonyms for tools and databases were merged and counted under a single keyword. IMPPAT was considered to be the method Indian Medicinal Plants, Phytochemistry and Therapeutics to extract bioactive compounds from a biological plant (IMPPAT) [19].

### Drug-Target Interaction Methods

The Network Pharmacology approach predicts the binding conformation of small-molecule ligands to the appropriate binding site of the target using 3D structural information on the compounds and protein targets [20]. The key hypothesis of this approach is that compounds with a high binding affinity at the binding site are likely to interact with the target [21]. The ligand-based approach predicts interactions by comparing a new ligand to known proteins ligands based on the hypothesis that similar molecules usually bind to similar proteins [22]. Drug target interaction method extracted from the Binding Database, the database that integrate drug-target interaction information from heterogeneous sources.

### IMPPAT

IMPPAT software was used to identify bioactive compounds in four herbs of *Panchaskar churn.* Canonical smiles of individual bioactive compounds were identified by using PubChem software [23].

### ADMETlab

ADMETlab 2.0 software was used to eliminate the bioactive compounds based on the parameters like DILI (Drug Induced Liver Injury), VD (Volume of Distribution), Carcinogenicity, HIA (Human Intestinal Absorption), Lipinski rule, Oral toxicity and Log P.

### BINDING DATABASE

Binding database software was used to identify the targets by using canonical smiles of identified bioactive compounds in four herbs of *Panchaskar churn* [24].

### CYTOSCAPE

Cytoscape 3.9.1 software was used to construct the network of identified targets with respect to bioactive compounds and to know the interactions between bioactive compounds and targets [25].

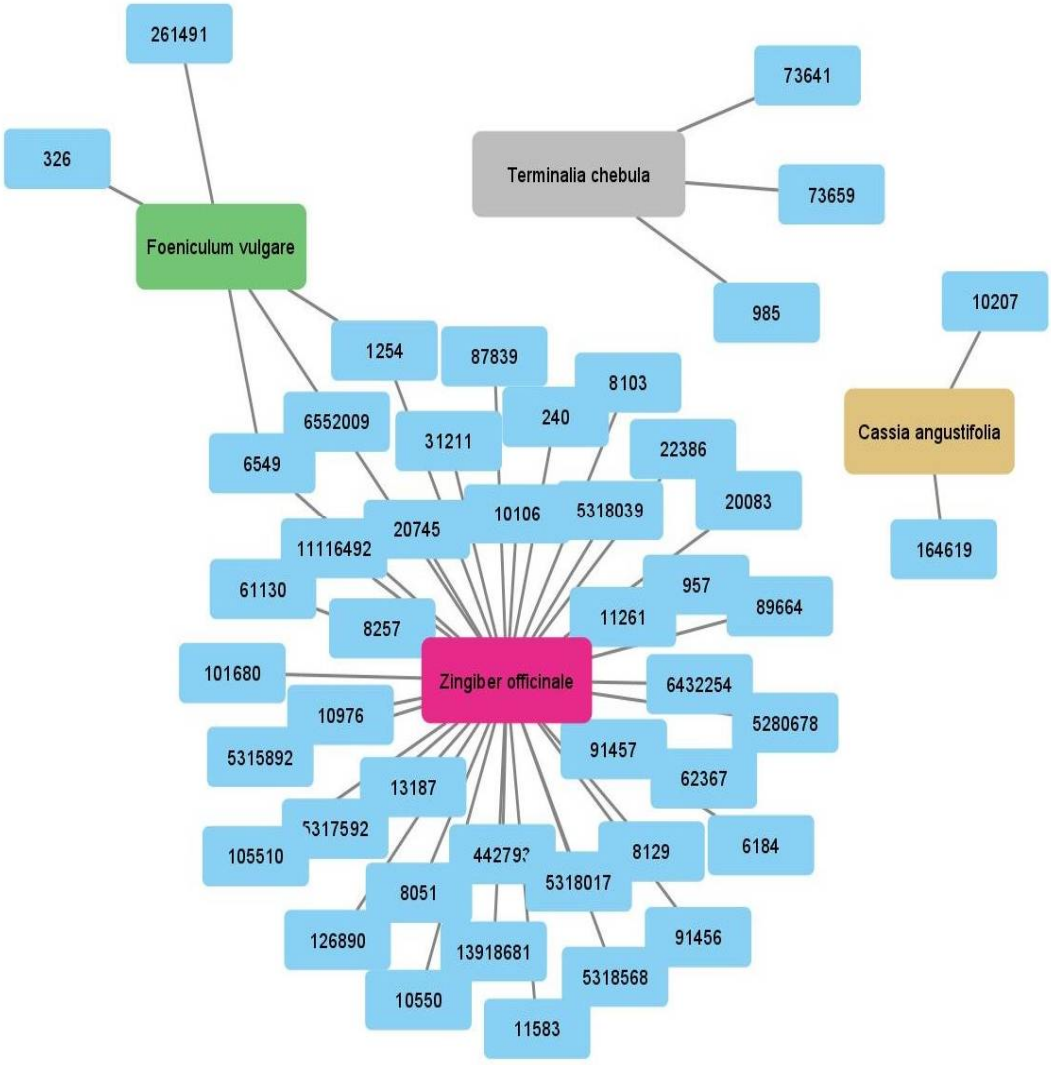


**Fig 2: PubChem id of identified compounds**

## RESULTS

### Identification of bioactive compounds from IMPPAT

*Panchaskar churn* consists of four herbs, namely *Cassia angustifolia* (Leaf), *Terminalia chebula* (Fruit), *Foeniculum vulgare* (Se), *Zingiber officinale* (Rhizome). A total of 393 bioactive compounds were identified in *panchaskar churn* by using IMPPAT 2.0, including 22 bioactive compounds in *Cassia Angustifolia*, 33 Bioactive compounds in *Terminalia chebula*, 54 Bioactive compounds in *Foeniculum vulgare*, and 284 Bioactive compounds in *Zingiber officinale*. Canonical smiles of individual bioactive compounds were identified by using PubChem software.

### Screening of bioactive compounds in ADMETlab

All identified canonical smiles of 393 bioactive compounds were screened by ADMETlab 2.0. by considering the parameters HIA (Human intestinal absorption), VD (Volume of distribution), Carcinogenicity, Oral toxicity, DILI (Drug-induced liver injury), Lipinski rule, LogP. Among these 393 bioactive compounds 31 bioactives were selected, from 4 herbs including 2 Bioactives were in CA, 3 Bioactives were in TC, 4 Bioactives were in FV, 22 Bioactives were in ZO.

**Table 2: Bioactives of CA, TC, FV, ZO.**

| S. No | BIOACTIVE COMPOUNDS | HERB |
|---|---|---|
| 1 | aloe-emodin | CA |
| 2 | D-pinitol | CA |
| 3 | arjunolic acid | TC |
| 4 | Maslinic acid | TC |
| 5 | Palmitic acid | TC |
| 6 | 4-isopropylbenzaldehyde | FV |
| 7 | d-borneol | FV |
| 8 | Thujone | FV |
| 9 | Menthol | FV |
| 10 | 2-Heptanol | ZO |
| 11 | Thujyl alcohol | ZO |
| 12 | 1,4-Cineole | ZO |
| 13 | 2-Hexanone | ZO |
| 14 | Zingerone | ZO |
| 15 | 2-Heptanone | ZO |
| 16 | Isogingerenone B | ZO |
| 17 | Gingerenone B | ZO |
| 18 | 2-Octanol | ZO |
| 19 | Myrtenal | ZO |
| 20 | 2-Nonanone | ZO |
| 21 | Camphene hydrate | ZO |
| 22 | beta-Eudesmol | ZO |
| 23 | d-Borneol | ZO |
| 24 | Gingerol | ZO |
| 25 | beta-thujone | ZO |
| 26 | (Z)-p-menth-2-en-1-ol | ZO |
| 27 | cis-sabinene hydrate | ZO |
| 28 | Menthol | ZO |
| 29 | trans-verbenol | ZO |
| 30 | 1-hydroxydecan-3-one | ZO |
| 31 | Hexahydrocurcumin | ZO |

**Target identification**

By using canonical smiles of 31 bioactive compounds 270 targets/genes were identified, including 18 were in CA, 62 were in TC, 34 were in FV and 156 were in ZO by using Binding Database software. These bioactive compounds are the major components of *Panchaskar churn*. The result of the selected 31 bioactive compounds from the four herbal medicines mentioned in below table.

**Table 3: Targets of bioactive compounds**

| S.no | Bioactive compound | PCID | Targets |
|---|---|---|---|
| 1 | Aloe emodin | 10207 | 5-LOX, MAOA, BCL-2, CYP19A1, CSNK2A1, CSNK2B, CYP1B1, ER, ESR2, MCL1, Integrase, LIMK1, NAAA, SIRT5, PSMB1, HPN, LCK |
| 2 | D pinitol | 164619 | GBA1 |
| 3 | arjunolic acid | 73641 | HSD11B1, HSD11B2, AKR1B10, CTSD, CD81, F10, ER, ESR2, GLO1, CES1, GAA, CDC25B, ELANE, RORC, NR1H3, PNLIP, PLA2, ALOX15, PTGS1, Protease, PRKCH, TF, RELA, PTPN1,2 |
| 4 | Maslinic acid | 73659 | HSD11B1, HSD11B2, AKR1B10, AR, CTSD, CD81, F10, ESR2, GLO1, CES1, GAA, CDC25B, MGLL, ELANE, NOS2, RORC, NR1H3, PNLIP, PPARA, PLA2, ALOX15, PTGES, Protease, PRKCH, TF, RELA, PTPN1, PTPN2 |
| 5 | Palmitic acid | 985 | FABP5, FABP4, FABP T94A, FFAR1, GPR84, KDM2A, SLC22A6, IpxC |
| 6 | 4-isopropylbenzaldehyde | 326 | MvfR |

| | | | |
|---|---|---|---|
| 7 | d-borneol | 6552009 | HSD11B2, AKR1B10, AR, CA2, POLA1, ESR2, GPBAR, GRIN2A, GRIN2B, FXR1, SHBG, SHH, NR5A1, UGT2B7 |
| 8 | Thujone | 261491 | HPD, AR, CYP19A, CA2, CFF12, GPBAR1, CES1 |
| 9 | Menthol | 1254 | HSD11B1, AR, CA2, ESR2, GPBAR1, GRIN2A, GRIN2B, FXR1, SHBG, SHH, UGT2B7 |
| 10 | 2-Heptanol | 10976 | CA2, SRC |
| 11 | Thujyl alcohol | 10550 | HSD11B1, AR, CA2, ESR2, GPBAR1, GRIN2A, GRIN2B, NR1H3, FXR1, SHBG, SHH, UGT2B7 |
| 12 | 1,4-Cineole | 10106 | CA2 |
| 13 | 2-Hexanone | 11583 | CES2, CSE1 |
| 14 | Zingerone | 31211 | HSD17B2, ACHE, BCA1, PDE4D, CA, CA1, CA2, ENR, NR3C1, HSP90AB1, IGF1R, ALOX5, LOX1.1, TUBA4A, TRPV1, TUBB2B |
| 15 | 2-Heptanone | 8051 | CA2, CES2, CSE1 |
| 16 | Isogingerenone B | 5318568 | TRPV1 |
| 17 | Gingerenone B | 5317592 | TRPV1, HDAC2,HDAC1O,TNKS |
| 18 | 2-Octanol | 20083 | CA2, SRC |
| 19 | Myrtenal | 61130 | AR, CYP19A1, DDIT3, ESR2, GPR55, NR3C1, HSF1, CES1 |
| 20 | 2-Nonanone | 13187 | CA2, CES , CES1 |
| 21 | Camphene hydrate | 101680 | HSD11B2, AKR1B10, AR, CA2, POLA1, ESR2, GRIN2A, GRIN2B |
| 22 | beta-Eudesmol | 91457 | LSS, CES1, MGLL, NR1H3, PTPN1, UGT2B7 |
| 23 | d-Borneol | 6552009 | HSD11B2, AKR1B10, AR, CA2, POLA1, ESR2, GRIN2A, GRIN2B, RORA, FXR1, SHBG, SHH, NR5A1, UGT2B7 |
| 24 | Gingerol | 442793 | HSD17B2, BCA1, PDE4D, CA, CA1, CA2,ALOX5, TRPV1 |
| 25 | beta-thujone | 91456 | HPD, AR, CYP19A1, CA2, F12, CES2, GPBAR, CES1 |
| 26 | (Z)-p-menth-2-en-1-ol | 13918681 | AR, SHBG, TBXA2R |
| 27 | cis-sabinene hydrate | 62367 | HSD11B1, AR, CA2, ESR2, GPBAR1, GRIN2A, GRIN2B, NR1H3, FXR1, SHBG, SHH, UGT2B7 |
| 28 | Menthol | 1254 | HSD11B1, AR, CA2, ESR2, GPBAR1, GRIN2A, GRIN2B, FXR1, SHBG, SHH, UGT2B7 |
| 29 | Trans-verbenol | 89664 | HSD11B1, ACHE, AR, CYP19A1, F10, ESR1, ESR2, GPR183, GRIN2A, GRIN2B, HIF1A, CYP51A1, LSS, MGLL, RORC, NR1H3, NRIH2, PPARA, PTGIR, PTGER1, PTGFR, SHBG, CYP17A1 |
| 30 | 1-hydroxydecan-3-one | 105510 | cqsS |
| 31 | Hexahydrocurcumin | 5318039 | LYPLA1, CA1, CA2, ABHD16A, ALOX5, TRPV1 |

**Compounds-Target Network Construction**

The result of the selected 31 bioactive compounds from the four herbs were presented in a network construction by using software Cytoscape 3.9.1. A total of 270 genes/targets were linked to the 31 identified compounds in the botanicals of *panchaskar churn*- CA, TC, FV, ZO. The resulting compound target gene network was illustrated in Fig 3 and 4.

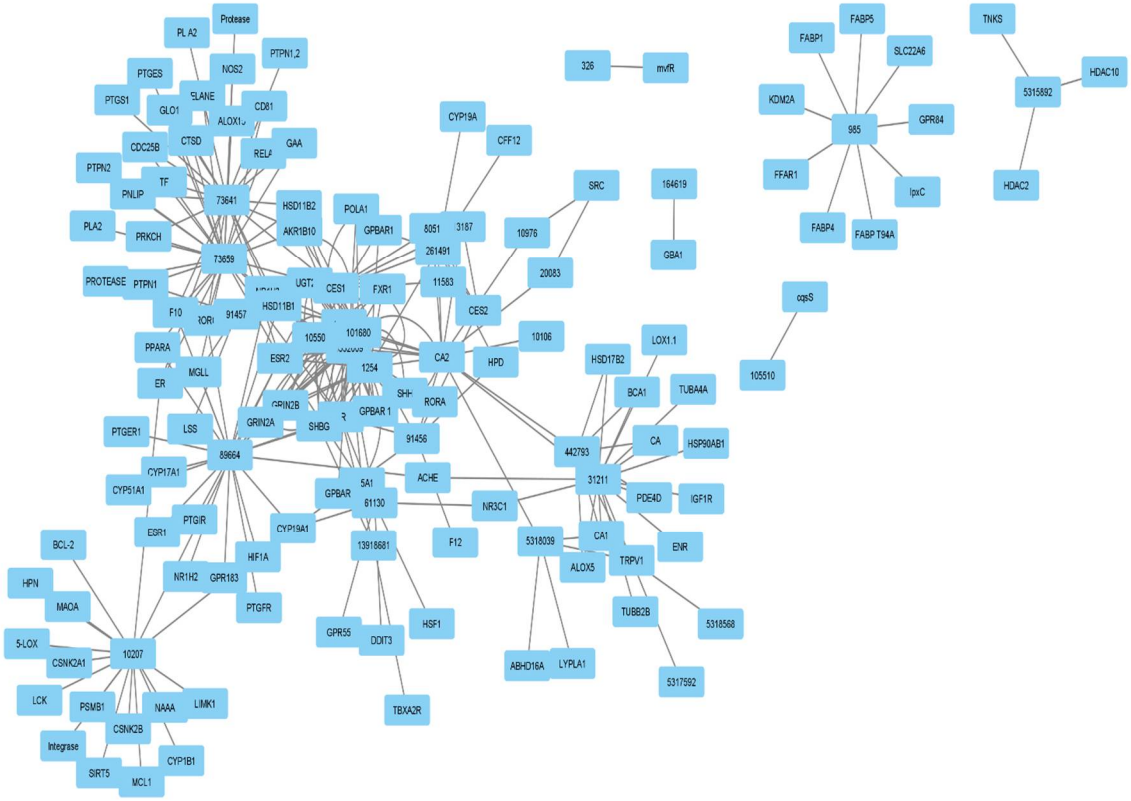


**Fig 3: Constructed network of *panchaskar churn* representing the PubChem ID and respected targets.**

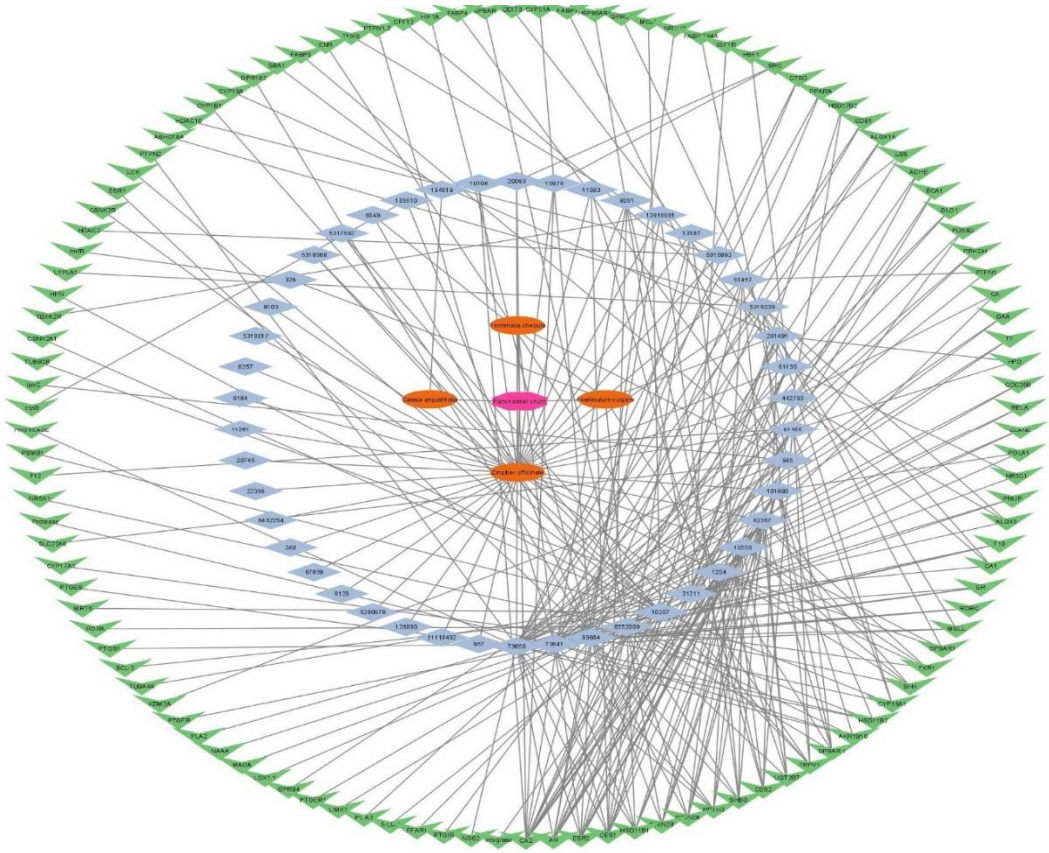

**Fig 4: Constructed network of *Panchaskar churn* representing the formulation, bioactives and their respective targets.**

## DISCUSSION

Network Pharmacology is essential for us to look for a cutting-edge and trustworthy curative system from a new perspective due to the occurrence of constipation and piles as well as the ineffectiveness of current allopathic therapy on treating complex-trait illnesses [26]. In order to treat complicated disorders, IMPPAT primarily focuses on maintaining the stability of the entire body by controlling communications among all components within the organisms. It is recognised that the complexity of the ingredients, targets, and mechanisms continues to impede the advancement of IMPPAT [27]. Moreover, network pharmacology has given researchers a fresh method for examining the pharmacological workings of IMPPAT. The complex of constituents, targets and mechanisms of herbal formulae have been explored in a number of studies using network pharmacology [28].

*Panchaskar churn* as a harmless healing herbal remedy, has actually been medically used for constipation and piles/hemorroids. The formulation is composed of 4 herbs i.e., Senna Patta (*Cassia angustifolia*) (leaf), Bhuni Choti Harre (*Terminalia Chebula*) (Fruit), Sonth (*Zingiber Officinale*) (Rhizome), Sounf (*Foeniculum Vulgare*) (Fruit) and Rock salt. Total 393 bioactive compounds were identified in CA, TC, FV, ZO based on the part of plant (IMPATT). Among 393 bioactive compounds 22 bioactives were in *Cassia Angustifolia*, 33 bioactives were in *Terminalia chebula*, 54 bioactives were in *Foeniculum vulgare* and 284 bioactives were in *Zingiber officinale*.

All identified bioactive compounds were screened to ADMET evaluation. By considering the ADMET parameters HIA (Human intestinal absorption), VD (Volume of distribution), Carcinogenicity, Oral toxicity, DILI (Drug-induced liver injury), Lipinski rule, LogP (ADMET), 31 bioactive compounds were selected from 393 bioactive compounds, including 2 bioactives were in CA, 3 bioactives were in TC, 4 bioactives were in FV and 22 bioactives were in ZO. These 31 bioactive compounds could target 270 genes were identified by using Binding Database software. The 2 bioactives were in CA could target 18 genes, 3 bioactives were in TC could target 62 genes, 4 bioactive were in FV could target 34 genes and 22 bioactives were in ZO could target 156 genes. The framework of these 31 bioactive compounds from the four herbs of PC were identified by using Cytoscape 3.9.1 software. Among 31 bioactive compounds, 4 bioactives namely aloe-emodin, maslinic acid, d-borneol and transverbenol were identified and considered to be potential as they may show their actions by targeting many genes.

## CONCLUSION

This research study establishes a solid framework for determining the effectiveness of multitarget and multicomponent therapies as well as identifying new treatment targets for constipation and piles. According to our network analysis, *Panchaskar churn* has multi targeting compounds that may act through different targets/genes and may be considered as novel therapeutic options against constipation and piles. Aloe-emodin, Maslinic acid, d-borneol, and Trans verbenol were identified as the main bioactive molecules found in *panchaskar churn* with high levels of target focussed based on their Protein Protein Interactions [PPI]. However the current study has provided a potential biological basics for the study of *panchaskar churn* in the treatment of constipation and piles but have to be screen for further pharmacological research studies to find the exact mechanisms.

## ACKNOWLEDGEMENT

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## COMPETING INTERESTS

The authors have declared that no competing interest exists.

## DECLARATION

This manuscript is neither published nor submitted for publication, in whole or in part, either in a serial, professional journal or as a part in a book which is formally published and made available to the public.

## Abbreviations

NP- Network pharmacology
PC- *Panchaskar churn*
CA- *Cassia angustifolia*
TC- *Terminalia chebula*
ZO- *Zingiber officinale*
FV- *Foeniculum vulgare*
THM – Traditional Herbal Medicine

IMPATT – Indian Medicinal Plants, Phytochemistry and Therapeutics
ADMET – Absorption, Distribution, Metabolism, Excretion and Toxicity
HIA – Human Intestinal Absorption
VD – Volume of Distribution
OT – Oral Toxicity
DILI – Drug-Induced Liver Injury
PPI – Protein – Protein Interactions

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